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Abstract

Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT

Joanne Blair,[1]* Andrew McKay,[2] Colin Ridyard,[3] Keith Thornborough,[4] Emma Bedson,[2] Matthew Peak,[5] Mohammed Didi,[1] Francesca Annan,[6] John W Gregory,[7] Dyfrig Hughes[3] and Carrol Gamble[2]

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Background: The risk of developing long-term complications of type 1 diabetes (T1D) is related to glycaemic control and is reduced by the use of intensive insulin treatment regimens: multiple daily injections (MDI) (≥ 4) and continuous subcutaneous insulin infusion (CSII). Despite a lack of evidence that the more expensive treatment with CSII is superior to MDI, both treatments are used widely within the NHS.

Objectives: (1) To compare glycaemic control during treatment with CSII and MDI and (2) to determine safety and cost-effectiveness of the treatment, and quality of life (QoL) of the patients.

Design: A pragmatic, open-label randomised controlled trial with an internal pilot and 12-month follow-up with 1 : 1 web-based block randomisation stratified by age and centre.

Setting: Fifteen diabetes clinics in hospitals in England and Wales.

Participants: Patients aged 7 months to 15 years.

Interventions: Continuous subsutaneous insulin infusion or MDI initiated within 14 days of diagnosis of T1D.

Data sources: Data were collected at baseline and at 3, 6, 9 and 12 months using paper forms and were entered centrally. Data from glucometers and CSII were downloaded. The Health Utilities Index Mark 2 was completed at each visit and the Pediatric Quality of Life Inventory (PedsQL, diabetes module) was completed at 6 and 12 months. Costs were estimated from hospital patient administration system data.

Outcomes: The primary outcome was glycosylated haemoglobin (HbA_{1c}) concentration at 12 months. The secondary outcomes were (1) HbA_{1c} concentrations of < 48 mmol/mol, (2) severe hypoglycaemia, (3) diabetic ketoacidosis (DKA), (4) T1D- or treatment-related adverse events (AEs), (5) change in body mass index and height standard deviation score, (6) insulin requirements, (7) QoL and (8) partial remission rate. The economic outcome was the incremental cost per quality-adjusted life-year (QALY) gained.

Results: A total of 293 participants, with a median age of 9.8 years (minimum 0.7 years, maximum 16 years), were randomised (CSII, $n = 149$; MDI, $n = 144$) between May 2011 and January 2015. Primary outcome data were available for 97% of participants (CSII, $n = 143$; MDI, $n = 142$). At 12 months, age-adjusted least mean squares HbA_{1c} concentrations were comparable between groups: CSII, 60.9 mmol/mol [95% confidence interval (CI) 58.5 to 63.3 mmol/mol]; MDI, 58.5 mmol/mol (95% CI 56.1 to 60.9 mmol/mol); and the difference of CSII – MDI, 2.4 mmol/mol (95% CI –0.4 to 5.3 mmol/mol). For HbA_{1c} concentrations of < 48 mmol/mol (CSII, 22/143 participants; MDI, 29/142 participants), the relative risk was 0.75 (95% CI 0.46 to 1.25), and for partial remission rates (CSII, 21/86 participants; MDI, 21/64), the relative risk was 0.74 (95% CI 0.45 to 1.24). The incidences of severe hypoglycaemia (CSII, 6/144; MDI, 2/149 participants) and DKA (CSII, 2/144 participants; MDI, 0/149 participants) were low. In total, 68 AEs (14 serious) were reported during CSII treatment and 25 AEs (eight serious) were reported during MDI treatment. Growth outcomes did not differ. The reported insulin use was higher with CSII (mean difference 0.1 unit/kg/day, 95% CI 0.0 to 0.2 unit/kg/day; $p = 0.01$). QoL was slightly higher for those randomised to CSII. From a NHS perspective, CSII was more expensive than MDI mean total cost (£1863, 95% CI £1620 to £2137) with no additional QALY gains (–0.006 QALYs, 95% CI –0.031 to 0.018 QALYs).

Limitations: Generalisability beyond 12 months is uncertain.

Conclusions: No clinical benefit of CSII over MDI was identified. CSII is not a cost-effective treatment in patients representative of the study population.

Future work: Longer-term follow-up is required to determine if clinical outcomes diverge after 1 year. A qualitative exploration of patient and professional experiences of MDI and CSII should be considered.

Trial registration: Current Controlled Trials ISRCTN29255275 and EudraCT 2010-023792-25.

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List of abbreviations

A&E	accident and emergency
AE	adverse event
BMI	body mass index
CDM	Center for Outcomes Research (CORE) diabetes model
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSII	continuous subcutaneous insulin infusion
CTU	Clinical Trials Unit
DECIDE	Delivering Early Care In Diabetes Evaluation
DKA	diabetic ketoacidosis
DPV	Prospective Diabetes Follow-up Registry
GP	general practitioner
HbA_{1c}	glycosylated haemoglobin
HDU	high-dependency unit
HRG	Healthcare Resource Group
HUI	Health Utilities Index
HUI2	Health Utilities Index Mark 2
HUI3	Health Utilities Index Mark 3
ICER	incremental cost-effectiveness ratio
$IDAA_{1c}$	insulin dose-adjusted HbA_{1c}
IDR	incidence density ratio
IDSMC	Independent Data and Safety Monitoring Committee
IQR	interquartile range
ITT	intention to treat
IU	international unit
LOCF	last observation carried forward
MCRN	Medicines for Children Research Network
MDI	multiple daily injections
MICE	multiple imputation with chained equations
NICE	National Institute for Health and Care Excellence
NPDA	National Paediatric Diabetes Audit
PAS	patient administration system
PedsQL	Pediatric Quality of Life Inventory
PICU	paediatric intensive care unit
PLICS	patient-linked information costing system
PRP	partial remission phase
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RN	research nurse
SAE	serious adverse event
SCIPI	SubCutaneous Insulin: Pumps or Injections?
SD	standard deviation
SDS	standard deviation score
T1D	type 1 diabetes
TDS	ter die sumendus
TMG	Trial Management Group
TSC	Trial Steering Committee

Plain English summary

People with type 1 diabetes cannot make insulin, a hormone that controls blood sugar levels. This type of diabetes is treated with insulin. Insulin can be given by injections at mealtimes, with additional injections in the evening and/or morning. Alternatively, insulin may be given by pumps that give a small amount of insulin continuously by a fine plastic tube and needle that goes under the skin.

Pump treatment costs more than treatment with injections. If pumps treat this type of diabetes better during childhood, then patients may not need as much medical care as adults. If there is no difference between injections and pumps, money may be better spent in other diabetes services.

We compared these two methods of treatment in 293 newly diagnosed children aged 7 months to 15 years. Half of the patients were treated with insulin pumps and half with injections. The method of insulin delivery was decided randomly; neither the doctor nor patient could choose which they received.

We measured how good each method was at controlling blood sugar levels, growth and weight gain, doses of insulin needed, side effects and quality of life (QoL) reported by parents and children. After 1 year, we compared these measurements. On average, children treated with continuous subcutaneous insulin infusion (CSII) had poorer blood glucose control, used more insulin and had more adverse effects than children who had multiple daily injections, but these results were not statistically significant. However, parents of children on CSII reported a small, but statistically significant, increase in QoL, but this was not observed in the child-reported QoL. In this study, pump treatment cost £1863 per patient per year more than injections. The results of our study are not necessarily true for children after the first year of diabetes. Further research is needed in children who have had diabetes for longer.

Scientific summary

Background

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood, affecting > 26,000 children and young people in the UK. The daily treatment burden of T1D is high, requiring the administration of subcutaneous insulin in doses calculated according to carbohydrate intake, energy expenditure and blood glucose readings. In the longer term, complications of T1D may result in blindness, renal failure, premature heart disease, stroke and amputation.

The risk of long-term complications of T1D is related to glycaemic control and is lower in patients treated with intensive insulin treatment regimens: multiple daily injections (MDI) (≥ 4 injections) or continuous subcutaneous insulin infusion (CSII). Despite a lack of evidence that the more expensive treatment with CSII is superior to MDI, both treatments are used widely within the NHS.

The current treatment costs for children and young people with T1D range from £52M to £70M per annum, but this could increase by 50% if all patients used CSII. Previous economic evaluations indicate CSII to be cost-effective in paediatrics, but these were reliant on data from small trials, which were rated as being at risk of bias, and the application of extensive modelling.

Objectives

Internal pilot study

Internal pilot objectives targeted recruitment and generalisability.

Primary objective

- To acquire an understanding of the acceptability of randomisation to MDI or CSII at diagnosis of T1D in children and young people.

Secondary objectives

- To define the characteristics of patients who consent and those who decline to participate.
- To generate data to confirm the standard deviation (SD) used in the sample size calculation of the full study.

Full study

The following objectives were addressed during the first year following the diagnosis of T1D.

Primary objective

- To measure glycaemic control, assessed by glycosylated haemoglobin (HbA_{1c}) concentration 12 months after diagnosis of T1D in participants receiving CSII compared with those receiving MDI.

Secondary objectives

To compare the following outcomes in children and adolescents receiving CSII with those receiving MDI:

- percentage of participants in each group with HbA_{1c} concentrations of < 7.5%
- incidence of severe hypoglycaemia

- incidence of diabetic ketoacidosis (DKA)
- change in height standard deviation score (SDS)
- change in body mass index (BMI) SDS
- insulin requirements (unit/kg/day)
- Pediatric Quality of Life Inventory (PedsQL) score
- cost-effectiveness based on the incremental cost per quality-adjusted life-year (QALY) gained.

Methods

Participants

Participants were recruited from 15 children's diabetes services in England and Wales with experience of treating ≥ 10 patients with CSII. Patients were eligible to participate in the study if they met the following inclusion criteria:

- The patient has newly diagnosed T1D.
- The patient is aged 7 months to 15 years.
- The parent/legal representative of the patient is willing to give consent for the study.
- The parent/legal representative of the patient is able to comply with the treatment regimen and study visits.

Participants with the following characteristics were excluded from the trial:

- previous treatment for T1D
- haemoglobinopathy
- co-existing pathology conditions likely to affect glycaemic control
- psychological or psychiatric disorders
- receipt of medication likely to affect glycaemic control
- allergy to a component of insulin aspart or insulin glargine
- sibling with existing T1D
- known thyroid condition in a non-euthyroid state
- known coeliac disease and inability to maintain a gluten-free diet.

Study procedures

Informed, written consent and, when appropriate, assent was obtained from parents/guardians and patients. Patients were randomised with 1 : 1 web-based block randomisation stratified by centre and age (7 months to < 5 years, 5 years to < 12 years and ≥ 12 years) to treatment with CSII or MDI. Owing to the nature of the interventions, blinding was not possible.

Screening logs were completed at each centre for all newly diagnosed T1D patients. Data were collected on age, sex, ethnicity and deprivation score. The reasons why patients were ineligible, why eligible patients were not approached to participate and why those who were approached declined to participate were recorded along with the dates and times when patients were approached about the SubCutaneous Insulin: Pumps or Injections? (SCIPI) study, when trial information was provided and when consent discussions took place.

The following data, when measured routinely, were collected at baseline:

- biochemical parameters at diagnosis: blood pH, blood glucose, HbA_{1c} concentration and thyroid function tests
- immunology studies: anti-islet cell and anti-glutamic acid decarboxylase antibodies, tissue transglutaminase or other antibody tests for coeliac disease
- growth: height and weight.

Randomised treatment started within 14 days of diagnosis of T1D. Starting insulin doses were calculated according to weight and age, and titrated against blood glucose readings in accordance with local protocols. To support this process, clinical practice guidelines and written patient information were shared from the lead centre for use by recruiting centres at their discretion.

Study visits coincided with clinic appointments at 3, 6, 9 and 12 months. At each visit, the following data were collected:

- HbA_{1c} concentrations
- adverse events
- height and weight
- insulin usage from general practitioner (GP) prescriptions, glucometer and insulin pump downloads (CSII) and patient-kept records (MDI).

The diabetes module of PedsQL was completed at 6 and 12 months.

The primary outcome was HbA_{1c} concentrations at 12 months. The secondary outcomes were (1) HbA_{1c} concentrations of < 48 mmol/mol, (2) severe hypoglycaemia, (3) DKA, (4) T1D- and treatment-related adverse events (AEs), (5) change in BMI and height SDS, (6) insulin requirements, (7) quality of life (QoL) and (8) partial remission rates. The economic outcome was the incremental cost per QALY gained.

Sample size

To achieve 80% power, a sample size of 143 participants in each group was required to detect a difference in means of 0.50, with common SD of 1.50, using a two-group *t*-test with a 0.05 two-sided significance level. An adjustment was made for 10% loss to follow-up, giving a total of 316 participants (158 per group).

Statistical analysis

Primary analysis used the intention-to-treat (ITT) principle. A 0.05 level of statistical significance and 95% confidence intervals (CIs) are used throughout. The statistical analysis plan was developed prior to analysis and is available as a separate document [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/081439/# (accessed 26 July 2018)]. All analyses were conducted using SAS® software (version 9.2; SAS Institute Inc., Cary, NC, USA). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.

When available, HbA_{1c} measurements from samples analysed centrally were used in preference to samples analysed locally. The primary outcome used least squares regression adjusted for age category and centre as a random effect. Binary outcomes are presented as relative risks. A per-protocol analysis was undertaken for the primary outcome to check the robustness of conclusions to major protocol deviations and a safety analysis was conducted on AE data, which included participants in the group to which they had received their insulin at the time of the event.

Economic evaluation

A cost–utility analysis estimated within-trial QALYs based on patients' or their parents' responses to the Health Utilities Index questionnaire, which was administered at 3-monthly intervals. Resource use was measured using questionnaires and by accessing prescription records and electronic patient-linked information costing systems. These included the purchase of pumps or MDI injection devices and associated consumables, cost of insulins and contact with health-care services, including with GPs, with school nurses, as a hospital inpatient, as an outpatient and accident and emergency (A&E) department attendances. National tariff and other standard unit costs were applied to calculate the total costs for the ITT population. A lifetime modelled extrapolation was planned if differences were apparent in HbA_{1c} concentrations between the intervention groups at 12 months. The differences between intervention groups in costs and QALYs were compared, with their joint uncertainty represented in cost-effectiveness acceptability curves.

Results

Recruitment data from the internal pilot study showed acceptable consent rates and no evidence of patient bias, and supported the parameters used in the sample size calculation. The Independent Data and Safety Monitoring Committee recommended that the trial progress to the full study. Data from patients recruited to the internal pilot study were included in the full study.

Participants

In total, 976 patients were diagnosed with T1D and assessed for eligibility in the 15 study centres, of whom 689 were eligible and approached for consent. Of these, 294 (42.7%) consented to participate in the trial; however, one participant withdrew consent for their data to be used immediately following randomisation. Of those patients who declined ($n = 395$), 36 (9%) cited a strong preference for CSII therapy and 259 (66%) cited a strong preference for MDI.

Age, sex and ethnicity did not differ between the group of patients who consented to participate and the group of patients who declined. The median deprivation score for study participants was 17.0 overall (minimum 1.62, maximum 77.23), 27.7 in those who declined owing to a strong preference for CSII (range 3.9–63.9) and 18.0 in those who declined owing to a strong preference for MDI (range 1.2–74.4). A higher score indicates a greater level of deprivation.

In total, 144 patients were randomised to CSII [mean age 9.0 years (SD 4.1 years); 71 (49.3%) female] and 149 patients were randomised to MDI [mean age 9.1 years (SD 4.1 years); 69 (46.3%) female]. Patient characteristics did not differ between treatment arms. All participants received their allocated interventions. One participant who was allocated to CSII and five who were allocated to MDI withdrew from the trial prior to the 12-month follow-up but allowed data collected up to their withdrawal to be used.

Glycosylated haemoglobin levels at 12 months

Intention-to-treat analysis

Data from 97% (CSII, $n = 143$; MDI, $n = 142$) of participants were available. The HbA_{1c} concentrations did not differ between treatment arms: CSII, mean 60.9 mmol/mol (95% CI 58.5 to 63.3 mmol/mol); MDI, mean 58.5 mmol/mol (95% CI 56.1 to 60.9 mmol/mol); and least mean squares-adjusted difference (CSII – MDI), 2.4 mmol/mol (95% CI –0.4 to 5.3 mmol/mol; $p = 0.09$).

Per-protocol analysis

Data from 52.2% (CSII, $n = 87$; MDI, $n = 66$) of participants were included. The HbA_{1c} concentrations did not differ between treatment arms and the direction of results were consistent with those obtained under the ITT analysis population: CSII, 60.2 mmol/mol (95% CI 56.4 to 63.9 mmol/mol); MDI, 59.3 mmol/mol (95% CI 55.3 to 63.3 mmol/mol); and the least mean squares-adjusted difference between treatment groups (CSII – MDI) was 0.9 mmol/mol (95% CI –3.2 to 5.0 mmol/mol; $p = 0.67$).

Percentage of patients with glycosylated haemoglobin levels within the target range 12 months after diagnosis

An ITT analysis was performed on two target values: (1) < 58 mmol/mol, the target set by the National Institute for Health and Care Excellence until August 2015, and (2) < 48 mmol/mol, the new target set in August 2015. Data for 97% (CSII, $n = 143$; MDI, $n = 142$) of participants were available for analysis.

There was no difference between treatment arms for either target. For the target HbA_{1c} value of < 58 mmol/mol: CSII, $n = 66$ (46.2%); MDI, $n = 78$ (54.9%); relative risk (CSII to MDI ratio), 0.84 (95% CI 0.67 to 1.06); and percentage difference (CSII – MDI), –8.8% (95% CI –2.9% to 20.4%). For < 48 mmol/mol: CSII, $n = 22$ (15.4%), MDI, $n = 29$ (20.4%); relative risk (CSII to MDI ratio), 0.75 (95% CI 0.46 to 1.25); and percentage difference (CSII – MDI), –5.0% (95% CI –14.0% to 3.9%).

Related adverse events

Eight episodes of severe hypoglycaemia were reported: six in participants who were treated with CSII and two in participants who were treated with MDI (relative risk 3.1, 95% CI 0.6 to 15.1; $p = 0.17$). Two episodes of DKA occurred in two participants, both of whom were treated with CSII (relative risk 5.2, 95% CI 0.3 to 106.8; $p = 0.24$).

Under the safety analysis population, there were 54 related AEs in 36 participants who were treated with CSII, of which 29 were related to the insulin pump; eight participants had infections at the site of catheter insertion. There were 17 related AEs in 16 participants who were treated with MDI, of which two events were related to injection device; there were no AEs related to injection sites. AEs relating to meter errors, carer errors and incidental illnesses were balanced more evenly across treatment arms.

Change in body mass index and height standard deviation score from diagnosis to 12 months following diagnosis

Data were available for 87% of participants: CSII, $n = 124$; MDI, $n = 132$. There was no significant difference in change in BMI or height SDS between study arms. The mean change in BMI SDS in the CSII group was 0.6 (SD 0.8) and in the MDI group was 0.5 (SD 0.8); the mean difference was 0.1 (95% CI 0.0 to 0.3; $p = 0.13$). The mean change in height SDS was –0.1 (SD 0.5) in the CSII group and 0.0 (SD 0.4) in the MDI group; the mean difference was –0.1 (95% CI –0.2 to 0.0; $p = 0.10$).

Insulin requirements

Data relating to insulin doses were available for 52% of participants (CSII, $n = 87$; MDI, $n = 64$); the least mean squares-adjusted difference for age demonstrated that insulin requirements were higher for participants in the CSII arm than for those in the MDI arm (difference, 0.1 unit/kg/day, 95% CI 0.0 to 0.2 unit/kg/day; $p = 0.01$).

Percentage of participants in each study arm in partial remission

Partial remission was defined as insulin dose-adjusted HbA_{1c} ($IDAA_{1c}$) level of ≤ 9. Data relating to insulin dose and HbA_{1c} concentration at 12 months were available for 51% of participants (CSII, $n = 86$; MDI, $n = 64$). The percentage of participants in partial remission at 12 months was higher in the MDI arm, but the difference was not statistically significant: CSII, 24.4% (21/86 participants); MDI, 32.8% (21/64 participants); and relative risk 0.74 (95% CI 0.45 to 1.24; $p = 0.28$).

Quality of life 12 months after diagnosis of type 1 diabetes

The PedsQL score (diabetes module), as reported by children at 12 months, was available for 71% or participants (CSII, $n = 104$; MDI, $n = 104$), with 26 children in each treatment group being too young to complete the questionnaire. Least mean squares-adjusted difference at 12 months (3.1, 95% CI –0.6 to 6.8) favoured CSII but the result was not statistically significant. Data were available from 86% of parents (CSII, $n = 128$; MDI, $n = 123$). The results for overall QoL favouring CSII, as reported by parents, were statistically significant at 12 months (least mean squares-adjusted difference 4.1, 95% CI 0.6 to 7.6). Parent- and child-reported results are largely consistent and should be considered against a difference of 5 being considered the minimum worthwhile.

Cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections

Patients randomised to the CSII arm had more than twice as many A&E department visits and inpatient stays relating to the management of T1D than those in the MDI arm. Over the 12-month study period, health-care professionals had a mean of 4.3 (95% CI 0.6 to 8.0) more contacts (texts, e-mails and telephone calls) with patients treated with CSII than with those treated with MDI. The mean total costs were £1863 (95% CI £1620 to £2137) higher for CSII than for MDI, with the majority of this difference being attributable to the additional cost of consumables (£1177) and the device (£520). There were no significant differences in QALYs between the CSII and MDI groups (mean difference –0.006 QALYs, 95% CI –0.031 to 0.018 QALYs). None of the sensitivity analyses affected the base-case result of CSII

being dominated by MDI. The probability of dominance was 69%, with no likelihood of CSII being cost-effective at a threshold of £30,000 per QALY.

Conclusions

Implications for health care

Study participants were recruited from diverse clinical settings, the retention rate exceeded 95% and the characteristics of those recruited to the study did not differ from the background population of patients diagnosed during this time. The findings of the study should therefore be applicable to the population of children treated in the NHS. Treatment with CSII has been embraced widely by the NHS, despite the high treatment cost and paucity of evidence of superior clinical outcomes. Our study shows that, during the first year of treatment, CSII is not associated with better clinical outcomes and is not cost-effective.

Implications for research

The generalisability of our data beyond the first year of diagnosis is uncertain. The observation period should be extended to determine whether or not treatment outcomes diverge over time and how factors, including child development, influence treatment decisions.

Patient advocates and many health-care professionals have a strong belief in the benefits of CSII treatment. In-depth qualitative research is required to learn more about the drivers influencing these preferences and how they alter as children age.

Trial registration

This trial is registered as ISRCTN29255275 and EudraCT 2010-023792-25.

Funding

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Chapter 1 Introduction

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood, affecting > 28,000 children and young people in the UK.[1] In Europe, the incidence of childhood T1D is rising, and it is estimated that between 2005 and 2020 the number of children diagnosed per year will increase from 15,000 to 24,400 and will double in children aged < 5 years.[2]

The treatment of T1D and its complications presents a considerable burden to patients, the NHS and society, and, as the number of affected patients increases, so do the projected costs. Currently, there is no cure for T1D, and so it is essential that insulin therapies are optimised to enable the best possible quality of life (QoL) for patients and effective use of NHS resources, while minimising the risk of acute and long-term complications.

The use of intensive insulin treatment regimens, in the form of multiple daily injections (MDI) (≥ 4) and continuous subcutaneous insulin infusion (CSII; or 'insulin pumps'), is associated with a reduction in the risk of developing long-term vascular complications of T1D[3] and both treatments are used widely in the NHS.

Treatment with MDI utilises insulin analogues with different pharmacokinetic properties. Once or twice a day, a long-acting insulin is administered using a pen injection device, which delivers insulin just beneath the skin into the subcutaneous tissues. This gives a relatively stable concentration of insulin throughout a 24-hour period. Additional injections of a short-acting insulin analogue are given every time ≥ 10 g of carbohydrates is consumed or when blood glucose concentrations rise above an acceptable level.

The term 'CSII' refers to the use of a small pump that infuses insulin, via a fine catheter and needle, to the subcutaneous tissues just under the skin. Using this technology, there is the potential to deliver insulin with a more physiological profile than can be achieved by treatment with MDI. Background insulin infusion rates can be increased and decreased to mimic the normal diurnal patterns of insulin secretion and physiological responses to exercise, illness, fasting, etc. Insulin boluses are infused by patients when > 5 g of carbohydrates is consumed or when blood glucose concentrations increase above an acceptable level. It seems logical to assume that the more physiological profile of insulin that can be achieved from CSII, together with a markedly reduced need to self-inject, would result in improved glycaemic control, reduced frequency and severity of hypoglycaemic events and improved QoL.

In 2008, a National Institute for Health and Care Excellence (NICE) guideline[4] recommended that children aged ≥ 12 years who cannot achieve glycosylated haemoglobin (HbA_{1c}) concentrations of < 8.5% without disabling low blood glucose concentrations (hypoglycaemia), despite a high level of care, should be offered a trial of CSII. Children aged < 12 years should be offered CSII therapy from diagnosis of T1D if MDI is considered impractical or inappropriate. Data from 28,400 paediatric patients were submitted to the 2015/16 National Paediatric Diabetes Audit (NPDA),[1] of whom 30% were treated with CSII, compared with 23% in the previous year. Of the 18,500 patients aged < 14 years, most would fulfil the age criteria for CSII therapy, and data reporting HbA_{1c} concentrations suggest that many of the older children would also qualify for treatment on the basis of poor glycaemic control.

Glycaemic control, intensive insulin therapy and complications of diabetes

In the short term, failure to manage T1D adequately may result in episodes of hypoglycaemia that may result in seizures in the most extreme circumstances or high blood glucose concentrations (hyperglycaemia), which may result in life-threatening episodes of diabetic ketoacidosis (DKA) if left untreated. However, it is the long-term vascular complications of T1D that have the greatest impact on morbidity, mortality and well-being. These can be broadly classified as macrovascular complications (coronary artery disease,

peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy and retinopathy).

The risk of acquiring these complications of T1D is directly related to glycaemic control, duration of T1D, insulin sensitivity and weight. By the time patients enter adult health-care services, many will have lived with T1D for ≥ 10 years, including a period of pubertal growth and development when changes in lifestyle, relationships within families and with peers, normal risk-taking behaviour and physiological insulin resistance make glycaemic control particularly challenging.

In 1993, The Diabetes Control and Complications Research Group[3] published conclusive evidence that both the degree and duration of hyperglycaemia are critical determinants of the risk of both microvascular complications and macrovascular complications. The median HbA_{1c} concentration was lower in patients treated intensively with either MDI or CSII (7.3%) than in patients treated using conventional insulin regimes (9.1%). In patients with established T1D who were observed over a period of 6.5 years, the risk of acquiring retinopathy or nephropathy was reduced by 76% and 39%, respectively, and of having a cardiovascular event was reduced by 41% in those treated with CSII or MDI. Glycaemic control exerted greatest influence on acquisition or progression of complications; however, following correction for the HbA_{1c} concentration, those patients who were treated with intensive regimes demonstrated a persistent benefit.

Data from historical paediatric cohorts have confirmed that the link between glycaemic control and microvascular complications is established in childhood.[5] Furthermore, there is a strong relationship between improved glycaemic control in children and young people and a fall over time in the prevalence of childhood-onset retinopathy and nephropathy.[6]

Glycaemic control in the first year after diagnosis has a long-lasting effect on glycaemic control in later life and, independently of glycaemic control, on the prevalence of complications. Two British, single-centre, retrospective studies, together reporting data from > 300 patients, reported that HbA_{1c} concentration at 6 months following diagnosis of T1D was an independent predictor of long-term glycaemic control up to 10 years later.[7,8] In a larger Swedish cohort of > 1550 children, HbA_{1c} concentrations at 3–15 months following diagnosis was related to poorer glycaemic control and increased risk of microalbuminaemia and retinopathy in young adult life.[9] These data highlight the importance of researching interventions that may influence glycaemic control during the critical first year of diagnosis.

Data relating to glycaemic control in childhood and macrovascular complications in adult life are sparse because of the long natural history of the disease. However, markers of an increased risk of cardiovascular complications have been validated and used to identify modifiable risk factors in childhood and adolescence. The SEARCH for Diabetes in Youth (SEARCH) study[10] has produced evidence that T1D affects (increases) arterial stiffness, a validated measure of risk for cardiovascular events and mortality in adult life, by late adolescence and early adult life. When data from a mixed cohort of patients with T1D and healthy control participants were analysed using multivariate analyses, other correlates of increased arterial stiffness included adiposity, blood pressure, lipid profile, ethnicity (black and hispanic ethnicities), blood pressure and microalbuminuria. In addition to the long-term vascular complications of poor glycaemic control, patients are subject to a number of health and social disadvantages during childhood. Hospital admission rates are nearly five times higher for children with T1D than for the background population, with the poorest children and those in the youngest age group being most likely to require admission.[11] Frequent episodes of severe hypoglycaemia and sustained hyperglycaemia have been associated with changes on functional brain magnetic resonance imaging, impaired memory and poorer cognitive outcomes.[12,13] Patients with poor glycaemic control may experience poor growth, particularly during puberty,[14] and poor glycaemic control has also been associated with an increased risk of childhood depression and use of antidepressants.[15]

Prevalence of vascular complications of type 1 diabetes

In the UK, data describing patient demographics, insulin treatment regimes, compliance with NICE guidelines and clinical outcomes are collected in the NPDA. In the 2015/16 NPDA report,[1] 9.7% of patients had microalbuminuria, an early marker of evolving diabetic nephropathy, and 13.8% had an abnormality on screening for retinopathy. Nearly one-third of patients were hypertensive, 20% had elevated blood cholesterol and 21% of those aged ≥ 12 years were obese. In a quantitative epidemiological systematic review of data from young adults (aged 18–30 years),[16] there was some evidence of diabetic retinopathy in 50% of patients, with more severe features presenting in 10% of patients. In the same population, one in six patients had evidence of evolving diabetic nephropathy and half were hypertensive.[16]

The data for adult patients for 2014/15 have yet to be reported in the National Diabetes Audit. However, the 2012/13 audit[17] reported that, compared with the background population, adults with T1D are 139% more likely to be admitted to hospital with angina, 94% more likely to be admitted to hospital with myocardial infarction, 126% more likely to be admitted to hospital with heart failure, 63% more likely to be admitted to hospital with a stroke, 400% more likely to be admitted to hospital for a major amputation, 817% more likely to be admitted to hospital for a minor amputation and 272% more likely to be admitted to hospital for renal replacement therapy.

There can be little doubt that the burden of T1D complications has a profound impact on the QoL and career prospects of patients. In a study of 91 young adults in their mid-thirties who had lived with T1D for nearly 30 years,[18] the mortality rate was 10 times higher than in a control population, owing to diabetic nephropathy and trauma, including suicide. People with T1D were less likely to be employed and more likely to need social welfare. Long-term complications of T1D were the primary predictor of an adverse outcome, with patients with T1D and no complications showing no significant differences from the control population.[18]

Treatment of childhood type 1 diabetes and glycaemic control in the NHS

In 2015/16, the NPDA reported data from approximately 28,400 patients aged < 19 years.[1] Intensive insulin regimes were used by 82% of patients: 54% were treated with MDI, having four or more insulin injections a day, and 28% were treated with CSII, an increase from 14% in 2011.

The NPDA also reports trends of improving glycaemic control over time, with the number of patients achieving the target HbA_{1c} concentration of < 58 mmol/mol, rising from 15.8% in 2012/13 to 27.0% in 2015/16. In the current NICE guideline for the treatment of childhood T1D, the target HbA_{1c} concentration has been reduced to 6.5% (48 mmol/mol).[19]

The *Paediatric Diabetes Best Practice Tariff Criteria*[20] were introduced in the UK in 2012. These allow for a payment of £3189 per patient per year, linked to the provision of core clinical services for paediatric T1D care. For most children's diabetes services, the additional funding made available by the *Paediatric Diabetes Best Practice Tariff Criteria*[20] enabled the recruitment of more specialist staff and the relative impact of this increase in resources compared with the introduction of CSII therapy on the improvement in glycaemic control reported in the NPDA is unknown.

National databases of children and young people with T1D are maintained in a number of other countries worldwide, enabling clinical outcomes to be compared between countries. In general, data from the UK compare poorly with those from other countries: a publication reported data from 2012[21] that were held in the NPDA data set, the Prospective Diabetes Follow-up Registry (DPV) from Germany and Austria, and the T1D Exchange database (T1D Exchange) from the USA. The data showed that glycaemic control was the poorest in the NPDA, which also had the lowest rate of CSII usage. In Britain, the disadvantage of poor

glycaemic control during childhood appears to persist into adult life. When HbA_{1c} concentrations were compared between national registries, reporting data from all age groups, from the UK, Germany, Denmark, Latvia and Austria, only Latvian patients had poorer glycaemic control.[22]

Evidence for the use of continuous subcutaneous insulin infusion in childhood

Evidence for CSII therapy comes from three areas: single-centre observational studies, national database reports and randomised controlled trials (RCTs).

Single-centre observational studies

A number of observational studies examining the effect of CSII therapy on glycaemic control have been published.[23–33] In these studies, authors report longitudinal data examining within-patient change in HbA_{1c} concentrations following the introduction of CSII or cross-sectional data comparing glycaemic control in patients treated with MDI with those treated with CSII. In general, the introduction of CSII therapy is associated with an improvement in glycaemic control in longitudinal observational studies,[23–27,34] coupled with a reduction in the number of severe hypoglycaemic episodes[23–25] and, in some studies, weight loss,[25,26] a reduction in insulin requirements[26,27] and an improvement in QoL.[23,24] Other authors have reported a transient improvement in glycaemic control, with a return to baseline values 6 months after the start of CSII therapy.[28] Transient improvements in markers of vascular function, blood pressure, HbA_{1c} concentration and glycaemic variability have also been reported 3 weeks after the introduction of CSII; however, at 12 months these measurements returned to baseline values and HbA_{1c} concentrations deteriorated.[29]

Cross-sectional studies report a less favourable effect of CSII on glycaemic control and QoL.[30,31,35] This difference may be explained by the fact that longitudinal studies followed patients who were changing from MDI to CSII, presumably because treatment outcomes with MDI were unsatisfactory, whereas those who were treated with MDI in cross-sectional studies are more likely to be satisfied with their treatment and to have acceptable glycaemic control.

Reduced glycaemic variability, but not HbA_{1c} concentration was reported in a cross-sectional study of 22 children treated with CSII compared with 26 children treated with MDI.[32] Insulin requirements and high-density lipoprotein cholesterol levels were also lower in those treated with CSII. Adolescents with established T1D treated with CSII for > 12 months have been reported to have reduced glycaemic variability and a reduction in the prevalence of microvascular disease compared with those treated with MDI.[33]

National database reports

An association between superior glycaemic control and CSII treatment has been reported in the DPV, T1D Exchange and NPDA data sets.[36] Higher rates of CSII use are reported in girls, whereas those from ethnic minorities and the most deprived patients are least likely to use CSII, even in health-care settings with universal funding.[37–39] In these studies, lower socioeconomic status and ethnicity were also predictors of poorer glycaemic control, even when the effect of CSII use was accounted for. This demonstrated that the characteristics of those who use CSII are the same as the characteristics that facilitate good glycaemic control, raising important issues of bias.

Randomised controlled trials

A number of small RCTs have been undertaken in children and young people,[2,7,35,40–48] and these are summarised in *Table 1*. A meta-analysis[49] of RCTs investigating the outcomes of children with T1D treated with CSII compared with those treated with MDI assessed six small studies.[34,35,44–47] The largest number of children included in a single study was 32. In total, 165 children and young people were included in these six studies, of which three included pre-school children only, and 78 children in total were aged > 5 years.

TABLE 1 Randomised controlled trials of CSII versus MDI in infants, children and young people with T1D

Study design	Observation period	Baseline characteristics				Between-treatment findings at study completion
		n	Age (years)[a]	HbA_{1c} (%)[a]	Duration of T1D (years)[a]	
Crossover RCT[40] (2003)	6 months for each arm	16	Median: 14.2 (range 14.1–17.5)	CSII: 8.6 ± 0.8 MDI: 8.5 ± 1.4	Not reported	No difference in HbA_{1c} concentrations or severe hypoglycaemia CSII: greater treatment satisfaction
Parallel RCT[35] (2004)	16 weeks	32	CSII: 12.5 ± 3.2 MDI: 13.0 ± 2.9	CSII: 8.2 ± 1.1 MDI: 8.1 ± 1.2	CSII: 6.8 ± 3.8 MDI: 5.6 ± 4.0	HbA_{1c}: 7.2% (CSII) vs. 8.1% (MDI); $p < 0.05$ Insulin doses: 0.9 unit/kg/day (CSII) vs. 1.2 unit/kg/day (MDI); $p < 0.003$ No difference in QoL
Parallel RCT[41] (1982)	6 days	16	CSII: 13.3 ± 4.0 MDI: 12.9 ± 2.4	CSII: 10.5 ± 2.9 MDI: 10.7 ± 1.1	Not reported	No significant difference in blood glucose (mean of seven samples/day) or 24-hour glycosuria MDI arm: more frequent morning hypoglycaemia
Parallel RCT[42] (2008)	CSII: 10.5 months MDI: 3.5 months, then 7 months for CSII	38	CSII: 10.0 ± 3.0 MDI: 10.0 ± 3.7	CSII: 8.3 ± 0.8 MDI: 8.4 ± 1.1	CSII: 5.6 ± 3.3 MDI: 4.7 ± 2.9	No significant difference in QoL or glycaemic control
Parallel RCT[43] (2008)	2 years	72	CSII: 11.8 ± 4.9 MDI: 12.3 ± 4.5	CSII: 8.2 ± 0.4 MDI: 8.4 ± 0.5	CSII: 12.2 ± 2.0 (number of days between diagnosis and entering the trial) MDI: 10.4 ± 1.7 (between diagnosis and entering the trial)	No difference in HbA_{1c} concentrations or severe hypoglycaemia Insulin doses: 0.7 unit/kg/day (CSII) vs. 1.1 unit/kg/day (MDI); $p = 0.001$ CSII: greater treatment satisfaction
Crossover RCT[43] (2004)	3.5 months for each arm	23	Arm A: 11.9 ± 1.4 Arm B: 11.9 ± 1.5	Arm A: 8.0 ± 1.1 Arm B: 8.3 ± 0.7	Arm A: 5.3 ± 1.9 Arm B: 6.3 ± 2.6	No significant difference in HbA_{1c} concentrations severe hypoglycaemia, DKA or QoL CSII: greater treatment satisfaction

continued

TABLE 1 Randomised controlled trials of CSII versus MDI in infants, children and young people with T1D (*continued*)

Study design	Observation period	Baseline characteristics				Between-treatment findings at study completion
		n	Age (years)[a]	HbA_{1c} (%)[a]	Duration of T1D (years)[a]	
Parallel RCT[44] (2004)	6 months	42	CSII: 3.8 ± 0.8	CSII: 9.0 ± 0.6	CSII: 1.8 ± 0.6	No difference in HbA_{1c} concentrations or severe hypoglycaemia
			MDI: 3.7 ± 0.7	MDI: 9.0 ± 0.6	MDI: 1.8 ± 0.6	
Parallel RCT[45] (2005)	24 weeks	26	CSII: 3.9 ± 0.4	CSII: 7.4 ± 0.5	CSII: 1.2 ± 0.3	No difference in HbA_{1c} concentrations or severe hypoglycaemia
			MDI: 3.8 ± 0.4	MDI: 7.6 ± 0.3	MDI: 1.6 ± 0.3	CSII: fathers reported greater improvement in QoL
Crossover RCT[46] (2003)	3.5 months for each arm	23	Median: 11.9 (range 9.3–13.3)	Median: 8.9 (range 6.1–10.1)	Median: 6.0 (range 2.5–11.0)	No difference in HbA_{1c} concentrations Continuous glucose monitoring during CSII: greater duration target range, less time in hypoglycaemic range, more frequent hyperglycaemic readings
Parallel RCT[47] (2005)	12 months	22	3.6 ± 1.0	8.0 ± 0.8	1.4 ± 0.6	No difference in HbA_{1c} concentrations QoL, episodes of severe hypoglycaemia or DKA
Parallel RCT[48] (2009)	CSII: 12 months	35	3.7 ± 0.8[b]	8.9 ± 0.6[a]	1.6 ± 0.6[a]	No difference in HbA_{1c} concentrations neurocognitive or parenting stress parameters
	MDI: 6 months for then 6 months for CSII					

a Values are mean ± SD, unless stated otherwise.
b Baseline characteristics were reported together in this study, rather than by arm.

In general, the period of observation was brief: ≤ 7 months in five studies. A statistically significant difference in HbA_{1c} concentrations between children treated with CSII and MDI was demonstrated at 3 months, but this was modest [–0.24%, 95% confidence interval (CI) –0.41% to –0.07%; $p < 0.001$]. The insulin dose, reported in three out of the six studies, was significantly lower in children treated with CSII [0.22 international units (IU)/kg/day, 95% CI 0.31 to 0.14 IU/kg/day; $p < 0.001$], whereas the incidences of ketoacidosis and severe hypoglycaemic events did not differ.

In summary, there is no conclusive evidence that treatment with CSII is or is not superior to MDI for glycaemic control or other clinical outcomes. This was in part attributable to the small number of patients studied, short observation periods and issues of bias.

Acceptability of continuous subcutaneous insulin infusion and multiple daily injections

The success of treatment with either MDI or CSII is likely to be heavily influenced by patients' and parents' views on the acceptability of each treatment modality. Studies examining this aspect of treatment are very limited. Data reporting parental stress and QoL in studies comparing clinical outcomes during treatment with MDI and CSII are summarised in *Table 1*.

Discontinuation rates for CSII are reported to be < 20%, implying a high level of satisfaction with CSII therapy.[50–52] Older children, girls and those with poor glycaemic control are more likely to revert to MDI. Reasons for discontinuing CSII therapy include greater sense of disease, difficulties in doing sports, poorer sense of well-being during CSII therapy, wearing an insulin pump, embarrassment, pain at the site of needle insertion, poor glycaemic control, fear and dislike of frequent blood glucose monitoring.[53–55]

Qualitative work undertaken in a study of 19 parents with children aged < 12 years who had changed from MDI to CSII reported the benefits of CSII therapy to include no longer having to administer painful injections, fewer dietary restrictions, improved quality of family life and improved glycaemic control.[56] When patients and parents were interviewed in another study, they also reported improved glycaemic control, in addition to increased lifestyle flexibility and participation in social activities, during CSII therapy.[57] However, parents also reported increased demands on them during CSII therapy, primarily relating to increased blood glucose monitoring. These data give only a limited insight into the acceptability of either treatment. It is likely that patients who participated in these studies changed from MDI to CSII treatment because MDI treatment was unsatisfactory, and studies of unselected cohorts of patients are required to examine acceptability of both treatments.

Costs of treatment of childhood type 1 diabetes and its complications

The cost of T1D to the NHS in the UK is significant: estimates of expenditure range from £1B to £1.8B per year,[58,59] and this is expected to rise further, and is projected to account for 2% of total NHS expenditure over the next two decades.[58] The proportion of this cost that is attributable to paediatric T1D services and the budgetary implications of switching patients to CSII is unknown. The number of children and young people aged < 19 years old in the UK with a diagnosis of diabetes is 31,500;[60] however, this may be a conservative estimate as not all children aged > 15 years old are managed in paediatric care settings and the true prevalence could be as high as 42,000. The majority of paediatric patients (95.1%) have T1D[60] requiring insulin therapy, which is currently administered by CSII in 24% of 10- to 14-year-olds and by MDI in 67%, with the remainder on mixed-methods treatment (three injections per day or fewer).[61] Based on published estimates of MDI and CSII costs[62] and the modelled costs of mixed insulins,[19] the current annual treatment costs for children and young people with T1D range from £52M to £70M. This would rise to between £79M and £106M if all were converted to using CSII. Additional costs relating to the management of T1D and its complications may be more than three times higher than treatment costs alone,[58] suggesting total current annual costs of between £179M and £241M, rising to between £272M and £366M if all patients used CSII.

In 2011, the year that the SubCutaneous Insulin: Pumps or Injections? (SCIPI) study opened to recruitment, it was also estimated that patients with T1D took 830,000 sickness days from work at a cost of £94M, and additional costs associated with T1D during work were > £91M. Premature death accounted for a further 37,000 lost working years, at an estimated cost of £0.6B.[58]

It is clear from these observations that T1D represents a significant threat to the well-being and life expectancy of affected patients, a significant cost to society in loss of productivity and economic output and an increasing threat to the NHS as its prevalence continues to rise, particularly in the youngest patients, who will require NHS treatment for the longest period of time. It is critical, therefore, to identify and manage factors that may influence the natural history of the disease and the risk of complications.

Rationale for research

The role of intensive insulin therapy in optimising glycaemic control and thereby reducing the risk of vascular complications of T1D is unquestioned. The optimal way in which to achieve this and the cost-effectiveness of the tools currently available are unknown. A number of observational studies and small RCTs have compared the outcomes of children and young people treated with CSII with those treated with MDI. However, in studies reported to date, there are concerns relating to bias, small patient numbers and short observation periods, and no RCT is directly applicable to the health-care environment in the UK.

Aims and objectives

The SCIPI study is a pragmatic RCT that compares the outcomes of infants, children and young people treated with CSII with those treated with MDI from the time of diagnosis of T1D. The study protocol was developed during a period in which children's diabetes care in the UK was changing rapidly with the widespread introduction of CSII.

The aim of the SCIPI study was to provide robust clinical data, together with a careful health economics appraisal, to inform the place of CSII therapy in the treatment of individual patients from diagnosis of T1D, and within national diabetes treatment strategies. This study compared CSII with MDI during infancy, childhood and adolescence to identify which treatment facilitates superior glycaemic control and to examine the impact that treatment modalities have on other predictors of vascular complications of T1D, adverse events (AEs) and QoL.

The study was designed with an internal pilot prior to progression to the full study. The objectives of the pilot and full study are detailed in the following sections.

Internal pilot study

Primary objective

- To acquire an understanding of the acceptability of randomisation to MDI or CSII at diagnosis of T1D in children and young people.

Secondary objectives

- To define the characteristics of patients who consent and those who do not consent to randomisation.
- To generate data to confirm the size of the standard deviation (SD) used in the sample size calculation of the full study.

Full study

Primary objective

- To compare glycaemic control, assessed by HbA_{1c} concentrations 12 months after diagnosis of T1D in infants, children and adolescents receiving CSII with those receiving MDI.

Secondary objectives

To compare the following outcomes in children and adolescents receiving CSII with those receiving MDI:

- clinical effectiveness
- safety
- growth
- quality of life
- cost-effectiveness.

Summary

Type 1 diabetes is a common disease of childhood, associated with complex treatment regimens and lifelong complications that pose a significant burden to individual patients. The cost to society and the NHS is also significant, as patients may not fulfil their potential in the workplace, may be more dependent on state assistance and may need intensive and expensive therapies throughout their lifetime.

There is the potential to modify the disease trajectory of patients by optimising treatment, particularly in children who will live with T1D for many years. Data from national registries suggest that children in the UK have less satisfactory glycaemic control than those in other health economies in which access to health care is also unrestricted. Some researchers have linked improved glycaemic control to higher rates of CSII use; however, the characteristics of those who are treated with CSII are the same as those that favour good glycaemic control, and the relative contribution of these factors is unclear.

Chapter 2 Trial design and methods

In developing the SCIPI study protocol, we aimed to address areas of potential bias identified in previous studies, to recruit a population of patients that was sufficiently large to enable us to be able to report, with confidence, differences in glycaemic control between treatment groups and to study secondary outcome measures that should give some insight into the evolving risk profile for macrovascular complications. A key part of the SCIPI study is the health economics assessment that examines how the additional investment in CSII may be offset against long-term health costs and QoL; this is reported separately in *Chapter 4*. To ensure acceptability of the study design and protocol across clinics in the UK, the study protocol was written in close collaboration with the Endocrinology and Diabetes Clinical Study Group of the Medicines for Children Research Network (MCRN). While developing the study protocol, we aimed to address three critical issues, discussed in the following sections.

Measures taken to address bias in patient populations

Previous RCTs have recruited patients with established T1D who are treated with MDI and randomised them to continue with treatment with MDI or to change to CSII. This recruitment strategy may introduce bias in favour of CSII, as patients who are satisfied with treatment with MDI and who have good glycaemic control are less likely to be approached or to participate in a study than those in whom treatment is less satisfactory. Furthermore, previous experience of treatment success or failure is likely to have an impact on the use of a treatment in the future. In order to address this potential bias, we recruited patients from the time of diagnosis of T1D.

We continued to address the internal pilot study objectives throughout the full study, by maintaining screening logs documenting patients' demographic data (age, sex, ethnicity and deprivation score derived from their postcode) and the reasons why patients were ineligible, why eligible patients were not approached to participate and why they declined. This enabled us to identify differences in the characteristics of those who consented to participate and those who declined and also to identify major barriers to recruitment.

Measures taken to address potential bias in treatment arms

There are two key areas of concern that were addressed within the SCIPI study design that could otherwise lead to bias between treatment arms.

Education

At the introduction of CSII therapy, there is a period of intensive education in which patients and their families consolidate their understanding of the relationship between insulin, carbohydrate consumption, exercise and periods of ill health. Intensive blood glucose monitoring is undertaken to determine the distribution of insulin infused across 24 hours, together with planned increases and decreases in infusion rates to account for periods of illness, exercise, etc.

In previous studies, it was not possible to determine whether the beneficial effect of CSII on glycaemic control was because of the method of insulin delivery or because of the period of intensive education and insulin dose titration. To address this educational imbalance, the SCIPI study protocol was designed such that both treatment arms were required to receive core diabetes education, as defined by the International Society for Pediatric and Adolescent Diabetes.[63] We then defined a minimum set of contacts between members of the diabetes team, patients and families in the period following diagnosis, and documented how long additional episodes of education or advice lasted. This information was included in the health economics assessment and used to detect imbalance in education and support across treatment arms.

Glucometers

The glucometers provided with insulin pumps advise patients of the dose of insulin required for a given quantity of carbohydrate, accounting for the patient's blood glucose concentration measured at that time. If blood glucose is measured when carbohydrates are not going to be consumed, and the blood glucose reading is high, the glucometer prompts the patient to take an additional dose of insulin, calculated to return the blood glucose to the target range.

At the time that the SCIPI study opened to recruitment, glucometers issued routinely to patients treated with MDI did not advise on insulin doses, placing them at risk of miscalculating doses or failing to recognise when additional doses may be required. In the SCIPI study protocol, we addressed this potential source of bias by ensuring that both treatment arms used the same F. Hoffman-La Roche AG's Expert glucometer (Basel, Switzerland).

Measures taken to ensure generalisability of study findings

It was important to generate data that could be used to inform local and national treatment strategies. To achieve this, the SCIPI study needed to recruit and retain participants who were representative of children and young people treated in the NHS. This required that the protocol be deliverable in a wide range of clinics and patient populations, including large clinics in university hospitals and smaller clinics in district general hospitals. To ensure a high retention rate, clinic, participant and parent acceptability needed to be high. The trial design aimed to achieve minimal disruption to normal clinic routines and appointments by drawing on clinical information collected routinely, ensuring that study visits coincided with the times of routine clinic appointments and including minimal additional tasks for patients and their carers.

Study design

The SCIPI study was designed as a pragmatic, open-label two-arm multicentre RCT comparing use of CSII with use of MDI in children and young people aged 7 months to 15 years who were newly diagnosed with T1D. The study included an internal pilot with a sample size of 30 participants to estimate the rate of consent to randomisation and to define the characteristics of recruited participants.

Progression from the internal pilot to the full study was based on the following criteria:

1. At least 50% of patients who are eligible and are invited to participate in the pilot study are successfully recruited.
2. Demographic characteristics that are significantly associated with glycaemic control (age, ethnicity, sex, deprivation score) are not significantly different in the group of patients who are recruited compared with those who decline.

The trial protocol has been published previously.[64] A schematic representation of the study design is given in *Figure 1*.

Ethics approval and research governance

This trial compared alternative methods of insulin delivery via Conformité Européenne (CE)-marked medical devices employed for their intended purpose; therefore, this trial was not considered to be a clinical investigation under *The Medical Devices Regulations 2002*.[65] The trial did fall within the remit of the European Union *Directive 2001/20/EC*,[66] transposed into UK law as *Medicines for Human Use (Clinical Trials) Regulations 2004*[67] as amended.

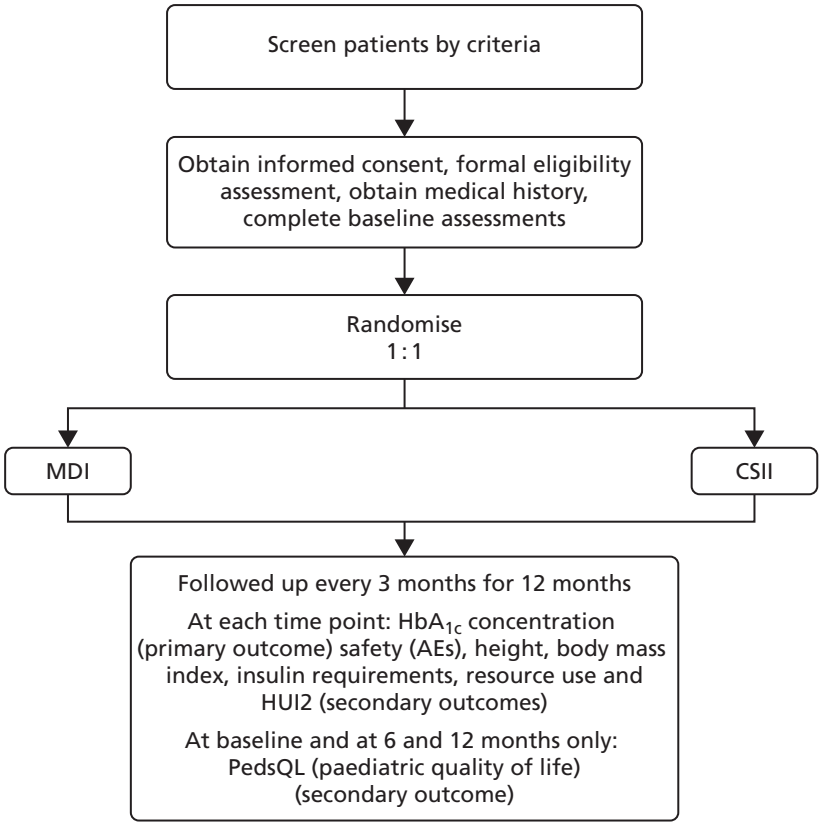

FIGURE 1 Study design. HUI2, Health Utilities Index Mark 2; PedsQL, Pediatric Quality of Life Inventory.

The protocol was approved by the Liverpool East Research Ethics Committee (reference number 10/H1002/80) and the Medicines and Healthcare products Regulatory Agency (clinical trial authorisation number 21362/0002/001-0001). The trial was funded by the National Institute for Health Research Health Technology Assessment programme (08/14/39) and included on the International Standard Randomised Controlled Trial Number registry (ISRCTN29255275) and the European Union Drug Regulating Authorities Clinical Trials database (EudraCT 2010-023792-25). Site-specific approval was obtained at all recruiting sites.

The study opened on protocol version 1.0 and the final approved version of the protocol was version 7.0. Protocol amendments are summarised in *Table 2*, and full details are provided in the study protocol (www.journalslibrary.nihr.ac.uk/programmes/hta/081439; accessed 15 February 2017).

Selection of study sites

Participants were recruited from 15 centres in England and Wales, which serve demographically diverse populations. To be eligible to participate in the study, centres had to have ≥ 10 participants treated with CSII within their clinic population and have sufficient resources to deliver the clinical aspects of the study protocol.

To inform our selection of recruiting centres, we drew on the experience of the investigators of the Delivering Early Care In Diabetes Evaluation (DECIDE) study,[68] another RCT that recruited paediatric patients at diagnosis of T1D. This study was delivered across eight children's diabetes centres. We invited the principal investigators who had recruited well to the DECIDE study to recruit patients to the SCIPI study.

Participants

The study recruited infants, children and young people who were newly diagnosed with T1D.

TABLE 2 Key protocol amendments

Protocol version (date)	Key amendments
2.0 (30 March 2011)	Inclusion criteria amendment to include patients and parents able to complete study material
	HbA_{1c} samples will be collected, analysed and destroyed according to local clinical practice rather than analysis at a central laboratory
	Pharmacovigilance: only related SAEs and related AEs will be reported for this trial. RUSAEs related to medical devices will be reported as per user vigilance reporting
3.0 (1 July 2011)	The time period to start the randomised treatment was changed from within 3–5 days to within 10 days. The study information will be provided and the consent should occur as close to the time of diagnosis as possible, ideally between the time of diagnosis (day 0) and day 5
	Timelines for providing information and approaching the patient for consent will be recorded on the screening log
	Internet randomisation system to be used instead of telephone, with randomisation envelopes as a backup. Up to this point all randomisations were completed using backup envelopes
	PedsQL (QoL) questionnaire booklets were removed from baseline and will only be administered at 6- and 12-month study visit
4.0 (17 August 2012)	Revision to the inclusion criteria, change to patients and parents able to comply with the treatment regimen and study visits
	Additions to exclusion criteria list: g. Known thyroid condition in a non-euthyroid state h. Known coeliac disease and unable to maintain a gluten-free diet Exclusions previously specified within the protocol but not numbered within the exclusion criteria
	Revision to the exclusion criteria: change to a. have a sibling with existing T1D rather than first degree relative
	Additional guidance and change to recruitment window period to 14 days and further guidance on patients being approached and consented as soon after diagnosis as possible
	HbA_{1c} samples to be collected, analysed and destroyed at a central laboratory
5.0 (21 January 2015)	Removal of the following from the eligibility criteria: patients aged ≥ 8 years are able to comply with the treatment regimen and study visits
	Addition of Omnipod® (Ypsomed Ltd, Escrick, UK) as a pump that can be supplied in line with normal clinical practice
	Addition of text permitting use of the insulin detemir (Levemir®, Novo Nordisk Ltd, Gatwick, UK)
6.0 (16 February 2016)	Update of contact members and their details
7.0 (1 August 2016)	Updated the HbA_{1c} concentration recommendations in line with the recent NICE guidance: change to the secondary objective. HbA_{1c} concentrations reduced from 7.5% to 6.5% and HbA_{1c} concentrations also provided in mmol
	Change to secondary end point – percentage of participants in each group with HbA_{1c} concentrations reduced from $< 7.5\%$ to $< 6.5\%$. Added partial remission and height as end points
	Outcomes may be presented as mmol/mol or equivalent %

PedsQL, Pediatric Quality of Life Inventory; RUSAE, related and unexpected serious adverse event; SAE, serious adverse event.

Inclusion criteria

Participants were considered for inclusion in the trial if they met the following criteria:

- they have newly diagnosed T1D using standard diagnostic criteria[69]
- they are aged 7 months to 15 years (inclusive)
- parent/legal representative of the patient is willing to give consent for the study
- parent/legal representative of the patient is able to comply with the treatment regimen and study visits.

Exclusion criteria

Participants with the following characteristics were excluded from the trial:

- previous treatment for diabetes
- haemoglobinopathy
- co-existing pathology conditions likely to affect glycaemic control (e.g. cystic fibrosis)
- psychological or psychiatric disorders (e.g. eating disorder)
- receipt of medication likely to affect glycaemic control (e.g. systemic or high-dose topical corticosteroid) or growth hormone therapy
- allergy to a component of insulin aspart (Novorapid®, Novo Nordisk Ltd, Gatnick, UK) or insulin glargine (Lantus®, Sanofi, Guildford, UK)
- sibling with existing T1D
- known thyroid condition in a non-euthyroid state
- known coeliac disease and inability to maintain a gluten-free diet.

Recruitment procedure

At the time that the SCIPI study opened, children's diabetes teams were notified within 72 hours of presentation of all infants, children and young people who were newly diagnosed with T1D. This possible delay in the identification of potential participants was addressed when the *Paediatric Diabetes Best Practice Tariff Criteria*[20] were introduced in 2011/12, shortly after the study opened. It is a requirement for centres receiving this additional payment that newly diagnosed patients are discussed with a senior member of the children's diabetes team within 24 hours of presentation, and that all new patients are seen by a member of the children's diabetes team on the next working day. All potentially eligible participants were therefore identified promptly.

Screening

Sites maintained detailed screening logs of all patients with newly diagnosed T1D. The screening logs collected data on the number of patients who:

- were assessed for eligibility at diagnosis of T1D
- met the study inclusion criteria
- were eligible at screening, were invited to consent and, subsequently, gave consent to participate
- were eligible at screening, were invited to consent but did not consent to participate in the study (with details of the reasons why consent was not given)
- were eligible at screening but consent was not sought (with details of the reasons for not seeking consent).

Dates and times of consent process milestones were also recorded along with the deprivation score calculated from patients' postcodes and ethnicity. These data were used to monitor and inform the recruitment process and to fulfil the internal pilot objectives.

Informed consent

Participants and families were given verbal and written information about the study at the time of diagnosis of T1D. Patient information leaflets were developed in collaboration with the MCRN Young Person's Advisory Group, 'Stand Up, Speak UP!' Three age-appropriate information leaflets for children

aged < 8 years, 8–12 years and > 12 years were prepared to ensure that study information was accessible to children of all ages. A separate information sheet was prepared for parents or legal guardians.

To support recruitment, and to address issues of patient preference, the SCIPI study team also produced a video. This was aimed at patients and families interested in taking part in the study, and gave a balanced patient's perspective of treatment with both methods of insulin delivery from some of the children, young people and their parents who had participated in the study. Four children and young people took part in the video; two were treated with MDI and two with CSII. The video was intended to be viewed after the SCIPI study had been introduced to the family by their diabetes team and the SCIPI information leaflet had been read.

The video was approved by the main research ethics committee in December 2013. The video went live on the SCIPI study website on 14 February 2014 (www.scipitrial.org.uk/families.html; accessed 15 February 2017) and was available for use at SCIPI study sites from 17 February 2014.

Consent was obtained by an appropriately trained and experienced member of the research or diabetes staff. The timing of consent was dependent on the needs and wishes of the patient and family. However, consent had to be obtained within a time frame that allowed for the randomised treatment to start within 14 days of diagnosis of T1D.

Randomisation, concealment and blinding

Once eligibility criteria were confirmed and informed consent, and assent when appropriate, had been obtained, participants were randomised to treatment with MDI or CSII, using a secure (24-hour) web-based randomisation programme controlled centrally by the MCRN division of the Clinical Trials Research Centre Clinical Trials Unit (CTU). A personal login (username and password), provided by the MCRN CTU, was required to access the randomisation system.

The randomisation code list was generated by a statistician within the MCRN CTU who was otherwise independent of the study, using random variable block sizes of 2 and 4. Participants were randomised to either MDI or CSII treatment in a ratio of 1 : 1, stratified by recruitment site and age using three bands (7 months to < 5 years, 5 years to < 12 years and ≥ 12 years).

The allocated treatment arm was communicated immediately to the patient and family and the treating health-care professionals, with the randomised treatment to start within 14 days of diagnosis.

Owing to the nature of the interventions, it was not possible to blind either the participants or clinical teams.

Treatment group allocation

Multiple daily injections

Participants randomised to treatment with MDI were treated with two insulin analogues: insulin aspart, a short-acting insulin, and insulin glargine or insulin detemir, long-acting insulin analogues. Insulin was delivered using 'pen' injection devices, which contain cartridges of insulin that are administered via a fine needle at the tip of the pen and injected using a plunger at the top of the pen.

Insulin aspart is a short-acting insulin analogue licensed for the treatment of T1D in adults, adolescents and children aged 2–17 years. It should be used in children aged < 2 years only under careful supervision; however, the rapid onset and offset of action of this insulin make it particularly attractive in the management of young children. For this reason, it is widely used in young children with T1D. Insulin aspart was administered every time ≥ 10 g of carbohydrates was consumed.

Insulin glargine is a long-acting insulin analogue, administered once or twice daily. It is not currently licensed for use in children aged < 6 years; however, the use of insulin glargine in this age group has been

associated with a reduction in hypoglycaemia and improved metabolic control.[70] For these reasons, it is widely used in MDI treatment regimens in UK paediatric practice.

In protocol version 5.0, the use of detemir was added to the long-acting insulin analogues permitted at the initiation of MDI therapy. This amendment was made in recognition that a number of recruiting sites started treatment with MDI, using insulin detemir at the time of diagnosis, and were reluctant to change to insulin glargine following randomisation to MDI. This insulin has been studied in the age group recruited to the SCIPI study and found to be safe and effective.[71]

Continuous subcutaneous insulin infusion

Insulin aspart was administered using CSII insulin pumps. The F. Hoffman-La Roche AG insulin pump (Basel, Switzerland) was selected at the start of the study, following discussion with the participating centres. This pump was used widely at the time the study opened, and participating centres had experience in its use. The use of the F. Hoffman-La Roche AG insulin pump also enabled us to use the same glucometer across both treatment arms. This glucometer includes a 'bolus wizard', which calculates insulin doses according to blood glucose readings and carbohydrate consumption. The use of this glucometer ensured consistency in the insulin bolus doses across treatment arms.

The F. Hoffman-La Roche AG insulin pumps and consumables were provided at a 25% discounted price for the study participants. However, this is a pragmatic study and treating clinicians were able to use other insulin pumps when this was considered to be in the patient's best interest. A small number of Medtronic (Medtronic Ltd, Minneapolis, MI, USA) and Omnipod® pumps (Ypsomed Ltd, Escrick, UK) were also used in some study centres. In these instances, patients used the appropriate glucometer for their pump.

Participants were given insulin aspart using basal insulin infusion with bolus doses of insulin aspart when ≥ 5 g of carbohydrate was consumed.

Starting dose calculations: multiple daily injections and continuous subcutaneous insulin infusion

The initial total daily dose of insulin was calculated from body weight. In prepubertal participants, a dose of 0.5 units/kg body weight/day was used, and in pubertal participants 0.7 units/kg body weight/day was used.

For the MDI arm, 50% of the calculated dose was given as a single injection either as insulin glargine or detemir, injected into the anterior-lateral aspect of the thigh, arm, abdomen or the upper outer quadrant of the buttocks.

For the CSII arm, 50% of the calculated dose was given as a continuous 24-hour infusion [0.5 × body weight (kg) ÷ 2 ÷ 24 = hourly rate].

The remaining 50% of the daily dose was given as three divided preprandial doses at mealtimes in both arms. If the doses were not equal, more insulin was given before breakfast and the evening meal than at lunchtime to account for diurnal variation in insulin sensitivity.

It was recommended that blood glucose readings should be undertaken at least four times a day: before breakfast, before the midday meal, before the evening meal and before supper/bed.

Insulin dose modifications

Correction doses were calculated according to the '100' rule.[72] Insulin doses were titrated according to home blood glucose readings, as per local routine clinical advice. The diabetes clinical team supported insulin dose titration according to participant needs. Telephone contact was also used as an opportunity to provide support and education regarding the management of T1D. The frequency and duration of all contact between participants and their local clinical service were logged. All participants and their parents had 24-hour telephone access for support and advice throughout the study, as is standard practice.

Participants on CSII treatment also had 24/7 access to the pump manufacturer's helpline for assistance for technical problems relating to the pump.

Education

At entry to the study, all participants completed a structured educational programme delivered to participants and their families in accordance with the standards of the International Society for Pediatric and Adolescent Diabetes.[63]

Participants and their families were educated in:

- type 1 diabetes
- the use and administration of insulin
- hyperglycaemia and correction doses
- hypoglycaemia symptoms and treatment
- exercise
- sick day rules
- carbohydrate counting
- the benefits of maintaining optimal glycaemic control for long-term health
- blood glucose monitoring.

All the participants were trained in the use of the MDI regimen and the F. Hoffman-La Roche AG Expert glucometer; participants undergoing CSII treatment were also trained in the use of CSII pumps.

Additional diabetic education was organised to suit individual needs of the participant and family. The dietitian met the participant and their family to assess their diet and educate them in carbohydrate counting. All contact was recorded within the participant follow-up.

To support recruiting sites in the initiation of CSII so soon after diagnosis of T1D, treatment guidelines and written patient information were available from the lead site. These resources were used at the discretion of the recruiting sites.

Baseline assessment

At entry to the study, we collected the following routine biochemical data recorded in medical case notes:

- blood pH at diagnosis
- blood glucose at diagnosis
- presentation with DKA
- glycosylated haemoglobin
- thyroid function tests
- tissue transglutaminase antibody titres, or other screening test for coeliac disease
- titres of anti-glutamic acid decarboxylase and anti-islet cell antibodies.

These baseline tests were not required as part of the SCIPI study protocol, but results were collected if available.

Baseline measurements of height and weight were recorded on the day that the participants commenced randomised treatment to allow for rehydration in participants who were dehydrated at diagnosis of T1D. The Health Utilities Index (HUI) questionnaire was completed and information was collected relating to prescribed concomitant medications. The Health Utilities Index Mark 2 (HUI2) was used for the base-case analysis and the Health Utilities Index Mark 3 (HUI3) (based on a Canadian tariff) was used in the sensitivity analysis.

Follow-up

Study visits were timed to coincide with the times of routine clinic appointments at 3, 6, 9 and 12 months from the date of randomisation. A window of 15 days either side of the appointment time was permitted to allow for holidays, clinic availability and other commitments. A schematic representation of follow-up assessments is given in *Table 3*. At each visit, permanent and temporary changes in the delivery of insulin were recorded under the heading 'Review of insulin use'.

Measures

Primary end point

The primary outcome measure was glycaemic control (HbA_{1c}) concentrations 12 months after diagnosis.

Capillary blood samples were collected from finger-pricks into small capillary tubes and were analysed in two separate locations. At study sites, most samples were analysed using portable instrumentation at outpatient clinics. Samples were also analysed at the clinical pathology laboratory in Alder Hey Children's NHS Foundation Trust. Samples were transported to the central laboratory through the post or via bespoke courier systems that ensure that the samples are received the next day.

Quality assurance of the measurement of glycosylated haemoglobin levels

Portable instrumentation is calibrated regularly with local laboratories. All laboratories involved in the measurement of HbA_{1c} concentrations are obliged to participate in external quality assurance schemes, ensuring that laboratories with equivalent equipment are able to produce results that are comparable to each other. For almost all HbA_{1c} measurements (local and central), the biochemical methodology employed was immunoassay.

Since June 2009, HbA_{1c} assays have been calibrated against the International Federation of Clinical Chemistry and Laboratory Medicine standardised values,[73] and centralised analysis should no longer be necessary; therefore, costs to support central analysis were not provided within the study budget. However, the preference in the trial design was for central analysis and this was included when funds were identified to support this (changed from local to central analysis in protocol version 4.0, August 2012).

To determine whether or not central analysis was required, a limits of agreement analysis was performed when 590 paired samples were available. Based on the results of this analysis,[74] samples continued to be analysed both locally and centrally.

Data from local samples were usually recorded in two units of measurement: mmol/mol and % (percentage of total haemoglobin). The HbA_{1c} concentration measured at the central laboratory was recorded in mmol/mol only. The following formula was used for conversion between the two units of measurement:

$$HbA_{1c}\ (\%) = \frac{HbA_{1c}\ (\text{mmol/mol})}{10.929} + 2.15. \quad (1)$$

Secondary end points

Percentage of participants in each group with a glycosylated haemoglobin level of < 48 mmol/mol at 12 months after diagnosis

At the time the SCIPI study protocol was written, the target HbA_{1c} concentration was < 58 mmol/mol. However, in the most recent NICE guideline, the target has been reduced to 48 mmol/mol.[19] This lower figure was used in our analysis to ensure that the findings are relevant to current clinical practice; however, as sites would have previously worked to the 58-mmol/mol threshold, the results for this are also presented.

TABLE 3 Trial assessments

Procedures	Time point					
	Baseline (randomisation)		Follow-up (months after randomisation)			
	Diagnosis	Prior to start of treatment	3	6	9	12
Assessment of eligibility criteria	✗					
Signed consent form	✗[a]					
Randomisation	✗					
Review of concomitant medications	✗		✗	✗	✗	✗
Review of insulin use (insulin requirements)						
Treatment diaries			✗	✗	✗	✗
Prescriptions			✗	✗	✗	✗
CSII pumps download			✗	✗	✗	✗
Blood glucose measurement	✗[b]		✗	✗	✗	✗
Blood pH measurement	✗					
Demographics	✗					
Study intervention		✗[c]				
Physical examination						
Height	✗		✗	✗	✗	✗
Weight	✗		✗	✗	✗	✗
Injection sites			✗	✗	✗	✗
Symptom-directed			(✗)	(✗)	(✗)	(✗)
Assessment of related AEs						
Incidence of severe hypoglycaemia			(✗)	(✗)	(✗)	(✗)
Incidence of DKA			(✗)	(✗)	(✗)	(✗)
Other AEs			(✗)	(✗)	(✗)	(✗)
Related to diabetes			(✗)	(✗)	(✗)	(✗)
Clinical laboratory						
HbA_{1c} analysis[d]	✗		✗	✗	✗	✗
Other routine tests[e] (e.g. chemistry, haematology, urinalysis)	(✗)		(✗)	(✗)	(✗)	(✗)
Questionnaires						
Participant-completed PedsQL				(✗)		(✗)
Parent-completed PedsQL				✗		✗
Participant-completed HUI Questionnaire[f]		(✗)	(✗)	(✗)	(✗)	(✗)
Parent-completed HUI Questionnaire[f]		✗	✗	✗	✗	✗
Resource use						
RN-completed CRF		✗	✗	✗	✗	✗

✗, the time point at which a procedure was performed; (✗), as indicated/appropriate; CRF, case report form; PedsQL, Pediatric Quality of Life Inventory; RN, research nurse.

a Recruiting staff were encouraged to provide information, discuss the study and obtain informed consent as close to the time of diagnosis as possible, ideally between the time of diagnosis and day 5 (diagnosis date + 5 days).

b Blood glucose at the time of diagnosis was measured as per local policy and the results recorded from patient medical records. It was measured by glucometer at the remaining time points.

c Study intervention: randomised treatment should be commenced within 14 days of diagnosis.

d Glycosylated haemoglobin was collected and analysed according to local clinical practice and a sample sent for central analysis.

e Routine clinical tests were conducted as part of routine clinical management and, when appropriate, results recorded from patient medical records.

f The HUI2 algorithm was used for the base-case analysis and HUI3 algorithm (based on a Canadian tariff) was used in the sensitivity analysis.

Incidence of severe hypoglycaemia

Severe hypoglycaemia was defined according to the criteria of the American Diabetes Association: a hypoglycaemic episode that required the assistance of another person to administer carbohydrate, glucagon or other treatments.[75]

Incidence of diabetic ketoacidosis

Diabetic ketoacidosis was defined according to the criteria of the European Society of Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society:[76] blood glucose level of > 11 mmol/l, with a venous pH of < 7.3 and/or bicarbonate concentration of < 15 mmol/l.

Change in body mass index standard deviation score

Height was measured using a fixed stadiometer and weight was measured using electronic scales. Body mass index (BMI) was calculated according to the formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}. \quad (2)$$

Standard deviation scores (SDSs) were derived from 2007 World Health Organization growth data.[77,78]

Insulin requirements (unit/kg/day)

Insulin usage was downloaded from F. Hoffman-La Roche AG's Expert glucometers for participants in both treatment arms. For participants who were treated with CSII, insulin usage was also downloaded from insulin pumps, and for participants who were treated with MDI, data were retrieved from patient-held records. Finally, to guard against significant over-reporting and for the health economics assessment, the general practitioner (GP) of the participant was contacted for details of issued prescriptions.

Percentage of patients in partial remission at 12 months

Rates of partial remission were calculated at each time point, according to insulin dose-adjusted HbA_{1c} ($IDAA_{1c}$) level. This measure is calculated according to the formula:

$$\text{IDAA}_{1c} = \text{HbA}_{1c} + 4 \times \frac{\text{daily insulin dose (unit)}}{\text{weight (kg)}}. \quad (3)$$

Health-related quality of life

Health-related QoL was assessed using version 3 of the diabetes module of the Pediatric Quality of Life Inventory (PedsQL) questionnaire,[79,80] completed at routine clinic appointments at 6 and 12 months. The questionnaire was not completed at baseline because patients and parents are asked to rate their experience of living with T1D in the previous month. Given that patients were recruited at diagnosis of T1D, these questions were not relevant.

The PedsQL has age-specific questionnaires to be completed by children (aged 5–7 years old, 8–12 years old and 13–16 years old). The parent-reported PedsQL includes an additional age band for children aged 2–4 years.

Sample size

A difference in HbA_{1c} concentration of 0.5% is widely recognised as the threshold used by the US Food and Drug Administration and the pharmaceutical industry to determine effectiveness of any new oral hypoglycaemic agents. A meta-analysis of 20 studies comparing CSII with MDI detected an improvement of 0.61% in adults, suggesting that, in addition to this estimate being the minimum clinically important, it is also a realistic difference to detect.[81–100] To achieve 80% power, a sample size of 143 in each group was required to detect a difference in means of 0.50, assuming that the common SD is 1.50 using a two-group

t-test with a 0.05 two-sided significance level. Allowing for 10% loss to follow-up increased the sample size to a total of 316 participants (158 per group). The estimate used for the SD in the sample size calculation was taken from an unpublished audit at Alder Hey Children's NHS Foundation Trust (Joanne Blair, Mohammed Didi, Princy P, Atrayee Ghatak, Alder Hey Children's NHS Foundation Trust, 2009, personal communication) based on children matching the inclusion criteria for this proposed study.

Statistical methods

The analysis and reporting of the SCIPI study was undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT)[101] and the International Conference on Harmonisation E9 guidelines.[102] The main features of the statistical analysis plan are included here with a full and detailed statistical analysis plan provided as a separate document [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/081439/# (accessed 26 July 2018)]. All statistical analyses were undertaken using SAS® software (version 9.2; SAS Institute Inc., Cary, NC, USA). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates US registration.

A two-sided *p*-value of ≤ 0.05 was used to declare statistical significance for all analyses. Similarly, all CIs were calculated at the 95% level. No adjustment for multiplicity was made to adjust the type 1 error rate for secondary outcomes. Relevant results from other studies already reported in the literature were taken into account in the interpretation of results.

The primary analysis followed the intention-to-treat (ITT) principle as far as practically possible; a secondary analysis using the per-protocol approach was conducted for the primary outcome. The purpose of the per-protocol approach is to consider the robustness of the conclusions reached from the analysis using the ITT principle, which includes protocol deviations.

Glycosylated haemoglobin, a continuous outcome, was compared between the trial groups using mixed-model regression with 12-month HbA_{1c} as the dependent variable, treatment group as an explanatory factor and the randomisation stratification variables (age group and centre) as covariates; centre was fitted as a random effect. The mean and SD of HbA_{1c} concentrations were reported for each age group and treatment group. The mean difference in HbA_{1c} concentrations and 95% CI between treatment groups was given as the estimated age group- and centre-adjusted treatment effect calculated by the fitted mixed-model regression. Central measures of HbA_{1c} concentration were used in preference to local measurements; local measurements were used if central ones were not available.

Secondary continuous outcomes were analysed as per the primary outcome methods. For binary outcomes, the number and percentage of participants with the outcome are reported overall and for each treatment group. The difference between groups is tested using the chi-squared test. Relative risks with 95% CI are presented.

The safety analysis data set contains all participants who were randomised and received at least one dose of insulin via the randomised treatment. Participants' AEs/serious adverse events (SAEs) were included in the treatment group the participant was actually receiving at the time of AE/SAE onset to take into account any participants who permanently changed their mode of insulin delivery at any point during the trial. The number of related AEs occurring and the number and percentage of participants involved were reported by treatment arm. The incidence rates of total numbers of AEs/SAEs were calculated for each treatment group in person-days using the incidence density ratio (IDR). The IDR is the number of patients with at least one new AE per population at risk in a given time period. The denominator is the sum of the person-time in years for each treatment group (accounting for treatment switches) of the at-risk population.

The statistical analysis of the data follows the standard operating procedures of the Clinical Trials Research Centre, which requires independent programming of the primary outcome and safety analyses by an independent statistician.

Study oversight and role of funders

The Trial Management Group (TMG), comprising the chief investigator, other lead investigators (clinical and non-clinical), members of the MCRN CTU and three parent contributors, was responsible for the day-to-day running and management of the trial. The membership of the oversight committees was suggested by members of the TMG to the trial funders and appointed by the funders with their constitution following funder requirements.

The Trial Steering Committee (TSC) consisted of an independent chairperson, Dr Peter E Clayton, two independent experts in the fields of diabetes and endocrinology, Dr Christine P Burren and Dr Ian Craigie, an expert in medical statistics, Professor Gordon D Murray, and a parent contributor, Mrs Christina McRoe. The role of the TSC was as the executive decision-making committee considering the recommendations of the Independent Data and Safety Monitoring Committee (IDSMC). Monitoring reports viewed by the TSC were not split by treatment group.

The IDSMC consisted of an independent chairperson, Professor Stephen Greene, plus two independent members, Professor John Wilding, an expert in the field of endocrinology, and Dr Arne Ring, an expert in medical statistics. The IDSMC was responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC provided recommendations to the TSC concerning the continuation of the trial and viewed accumulating data split by treatment group.

Chapter 3 Results

Recruitment

The study opened to recruitment on 16 May 2011 and was closed on 30 January 2017.

At the outset of the study, we planned to recruit 316 patients within 30 months across eight study sites. The recruitment rate had been informed by the DECIDE trial[68] and the study sites were selected to build on the experience and expertise acquired by local researchers during the DECIDE trial.

All study sites had to secure funds to meet the excess treatment costs of the study protocol. This process incurred some considerable delays, and in some centres was not possible. Recruitment rates were also slower than expected and, consequently, the recruitment curve was revised in month 18 to allow for an additional 12 months of recruitment and again in month 40 to allow a further 6 months. The number of study sites was increased from 8 to 15. The recruitment graph showing the initial, and revised, predictions and the observed recruitment numbers is displayed in *Appendix 1*.

To increase recruitment, key protocol amendments were made (protocol version 3.0 to 4.0) that increased the permitted time window for recruitment from diagnosis to 14 days and softened eligibility criteria to place emphasis on ability to comply with treatment regimens rather than complete study questionnaires and to support inclusion of children with parents with T1D but to maintain exclusion of siblings with T1D.

To optimise consent rates, screening log data were used to inform the recruitment strategy. Screening data indicated that patients who consented to participate were approached sooner after diagnosis than those who declined. In the light of these data, clinical teams and research nurses (RNs) were encouraged to share information about the study as soon as possible following diagnosis.

In total, 976 patients were diagnosed with T1D in the 15 study centres in England and Wales during the 48-month recruitment period, of whom 98 (10%) did not meet the study eligibility criteria. One hundred and eighty-nine patients (22%) were not approached about participation. Of these, 115 (61%) were considered to be unsuitable by treating clinicians for reasons other than the study exclusion criteria, 52 patients (28%) were not approached because staffing levels at the site were too low at the time of diagnosis to deliver the study protocol and no reason was recorded for 22 (12%). Of the remaining 689 patients, 294 (42.7%) consented to participate in the study; however, one randomised participant withdrew consent for their data to be used immediately following randomisation, leaving 293 randomised participants.

Patients and families were invited to share their reasons for declining to participate in the study. The main reason given was patient preference for one of the trial arms. Strong patient preference had been expected at the design stage, and of the 395 eligible participants who declined consent, 36 (9%) cited a preference for CSII therapy and 259 (66%) cited a preference for MDI.

In response to this strong patient preference and to support an informed decision, we made a short film in which four SCIPI study participants (two randomised to CSII and two randomised to MDI) and their parents shared their experiences of diagnosis and living with T1D and the treatment in each of the study arms. Although the film was generally well received, we did not observe any increase in recruitment rates following its introduction and the issue of patient preference persisted throughout the trial.

A CONSORT flow diagram illustrating the pathway of patients from diagnosis to consent and randomisation and through the study protocol is given in *Figure 2*.

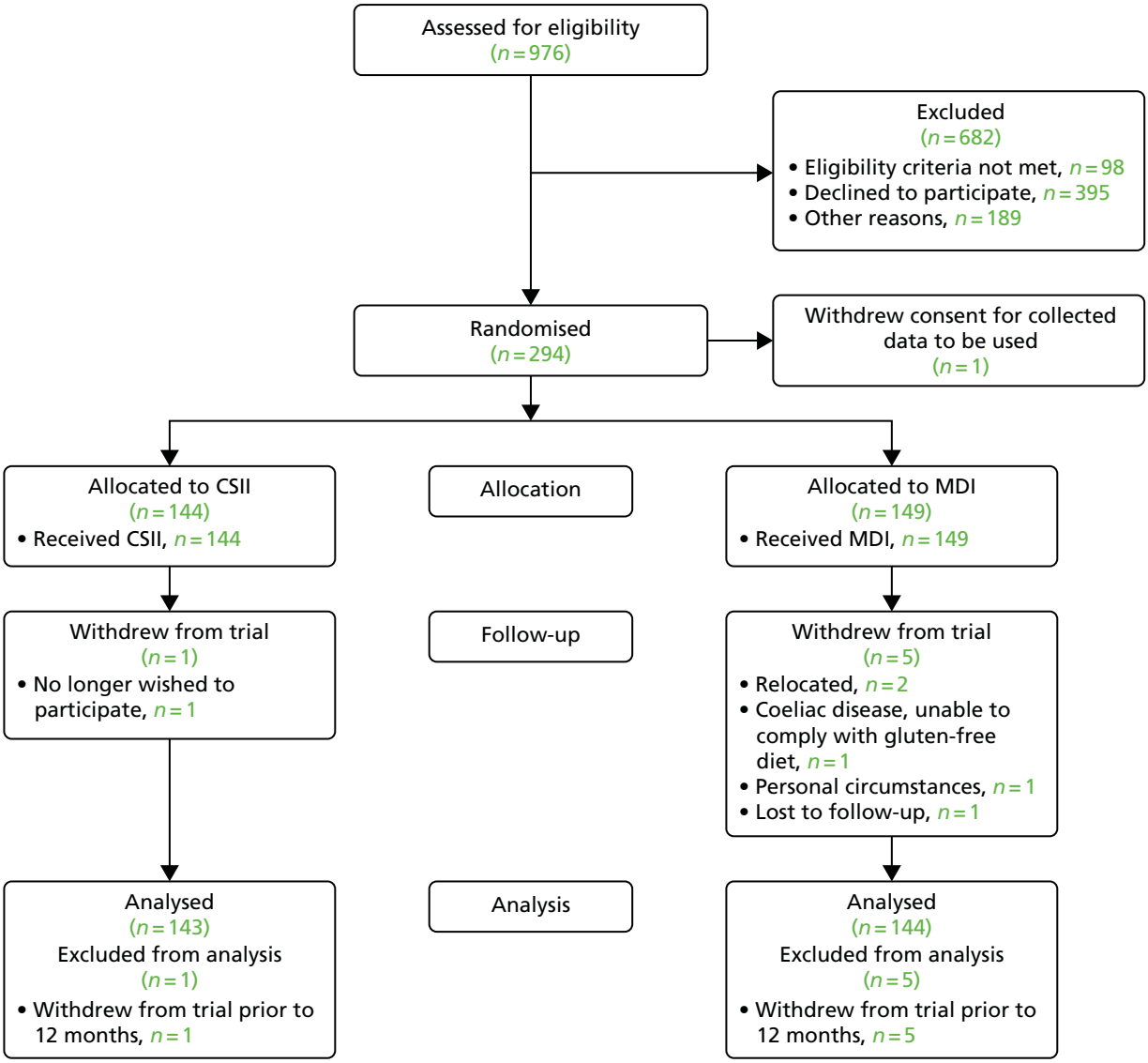

FIGURE 2 The CONSORT flow chart.

The purpose of the SCIPI study was to generate evidence that could be applied to the population of patients treated in children's diabetes services in the NHS. For this reason, it was important to demonstrate that patient characteristics, in particular those known to be associated with glycaemic control, did not differ between those who consented and those who declined to participate. The baseline characteristics of patients who were invited to participate in the study are given in *Appendix 1*, *Table 28*. There was no difference in age, sex or ethnicity between the group of patients who consented and the group of patients who declined. The median deprivation score for those who declined because they had a strong preference for CSII was 27.7 (range 16.6–63.9), compared with 17.0 (range 1.62–77.23) for those who consented and 17.96 (range 1.18–74.35) for those who stated a strong preference for MDI.

Internal pilot

The internal pilot was planned after 30 patients had been recruited. Of the 89 eligible patients approached for consent, 30 provided consent and 59 declined (33.7% consent rate, 95% CI 23.9% to 43.5% consent rate). The first patient was randomised on 31 May 2011, and 30 patients were randomised by 3 July 2012. A review of the consent rates by recruiting centre identified lower consent rates in one centre that started patients on

three daily injections at diagnosis, rather than MDI. Excluding this site, the consent rate increased (26/60 patients; 43.3%, 95% CI 30.8% to 55.9%). Screening data comparing characteristics of eligible consenting participants did not differ from those declining for age, sex, ethnicity or deprivation score. A review of the SD used in the sample size calculation to the accrued data indicated that the study should continue to the planned sample size. The recommendation of the IDSMC was that the SCIPI study should progress to the full study.

Baseline comparability

There was no difference in age, sex, ethnicity or deprivation score between treatment arms (*Table 4*). Baseline data also showed that auxological and biochemical characteristics did not differ between treatment groups at baseline (*Table 5*).

The measurement of autoantibodies was determined by local protocols, with some centres testing only patients in whom the diagnosis of T1D was felt to be uncertain. Eleven patients randomised to the MDI arm tested positive for coeliac disease on antibody testing, compared with four randomised to the CSII arm.

TABLE 4 Baseline demographics

Demographic variable	Treatment arm		Total
	CSII	MDI	
Age at randomisation (years)			
n (missing)	144 (0)	149 (0)	293 (0)
Median (IQR)	9.9 (5.7–12.2)	9.4 (5.8–12.5)	9.8 (5.7–12.3)
Minimum, maximum	0.8, 16	0.7, 15.4	0.7, 16
Age category, *n* (%)			
n (missing)	144 (0)	149 (0)	293 (0)
7 months to < 5 years	33 (22.9)	32 (21.5)	65 (22.2)
5 years to < 12 years	71 (49.3)	76 (51)	147 (50.2)
12 years to 15 years	40 (27.8)	41 (27.5)	81 (27.6)
Sex, *n* (%)			
n (missing)	144 (0)	149 (0)	293 (0)
Female	71 (49.3)	69 (46.3)	140 (47.8)
Male	73 (50.7)	80 (53.7)	153 (52.2)
Ethnicity, *n* (%)			
n (missing)	143 (1)	146 (3)	289 (4)
Asian or Asian British	4 (4.2)	7 (6.1)	10 (5.6)
Black or British black	0 (0)	3 (2.1)	3 (1)
British white	124 (86.7)	118 (80.8)	242 (83.7)
Mixed	4 (2.8)	6 (4.1)	10 (3.5)
Other white	9 (6.3)	10 (6.9)	19 (6.0)
Deprivation score[a]			
n (missing)	137 (7)	143 (6)	280 (13)
Median (IQR)	19.4 (8.9–37.9)	14.7 (7.8–31.8)	17 (8.4–35.8)
Minimum, maximum	1.8, 77.1	1.6, 77.2	1.6, 77.2

IQR, interquartile range.
a Deprivation score range: 0–100, with 100 indicating greater deprivation.

TABLE 5 Baseline auxological and biochemical characteristics

Demographic variable	Treatment arm		Total
	CSII	MDI	
BMI SDS			
n (missing)	124 (20)	132 (17)	256 (37)
Mean (SD)	0.2 (1.3)	0.1 (1.4)	0.1 (1.3)
Median (IQR)	0.2 (–0.7 to 0.9)	0.1 (–0.8 to 1)	0.2 (–0.8 to 1)
Minimum, maximum	–2.9, 4.2	–4.6, 3.5	–4.6, 4.2
Height SDS			
n (missing)	124 (20)	132 (17)	256 (37)
Mean (SD)	0.3 (1.1)	0.3 (1.1)	0.3 (1.1)
Median (IQR)	0.1 (–0.4 to 1.1)	0.4 (–0.3 to 1.1)	0.3 (–0.4 to 1.1)
Minimum, maximum	–2.3, 3.3	–4.8, 2.4	–4.8, 3.3
Local HbA_{1c} measurement (mmol/mol)			
n (missing)	122 (22)	122 (27)	244 (49)
Mean (SD)	105.9 (24.2)	103.6 (26.3)	104.7 (25.2)
Median (IQR)	105 (87 to 122)	103 (83 to 126)	104.7 (85.5 to 125)
Minimum, maximum	58, 184	55, 172.1	55, 184
Central HbA_{1c} measurement (mmol/mol)			
n (missing)	64 (80)	71 (78)	135 (158)
Mean (SD)	101.2 (24.9)	96.4 (24)	98.7 (24.4)
Median (IQR)	102.5 (81.5 to 127)	93 (79 to 119)	100 (80 to 126)
Minimum, maximum	38, 130	50, 130	38, 130
HbA_{1c} concentration[a] (mmol/mol)			
n (missing)	132 (12)	131 (18)	263 (30)
Mean (SD)	104.6 (24.4)	102.6 (26.7)	103.6 (25.5)
Median (IQR)	105 (87.5 to 127)	103 (81 to 127)	105 (84 to 127)
Minimum, maximum	38, 184	50, 172.1	38, 184
Blood glucose (mmol/l)			
n (missing)	141 (3)	146 (3)	287 (6)
Mean (SD)	26.8 (9.2)	26.9 (10)	26.9 (9.6)
Median (IQR)	26.2 (20.2 to 32.5)	25.6 (19.5 to 32.6)	25.7 (19.7 to 32.5)
Minimum, maximum	5.1, 56.0	5.7, 69.5	5.1, 69.5
Blood pH			
n (missing)	127 (17)	133 (16)	260 (33)
Mean (SD)	7.3 (0.2)	7.3 (0.1)	7.3 (0.2)
Median (IQR)	7.4 (7.3 to 7.4)	7.4 (7.2 to 7.4)	7.4 (7.3 to 7.4)
Minimum, maximum	6, 7.6	6.8, 7.5	6, 7.6

IQR, interquartile range.
a When available, central laboratory HbA_{1c} measurements were taken in preference of local laboratory HbA_{1c} measurements.

Retention and adherence

Figure 3 summarises the time point and number of patients who made a permanent change to their randomly allocated insulin delivery method, the time point and number of patients who decided to end their follow-up in the SCIPI study and the number of patients who attended each scheduled follow-up. In total, only six participants withdrew from the SCIPI study prior to the 12-month follow-up, and all remaining 287 patients (97.0%) attended the 12-month follow-up visit. See *Figure 2* for a summary of the reasons for withdrawals.

Permanent changes to insulin delivery

All participants initially received their insulin via their randomly allocated device.

Twenty-two patients (15%) randomised to CSII changed to MDI, and 31 patients (21%) randomised to MDI changed to CSII. *Table 6* summarises the time point and age group of participants who switched between treatment arms.

In the youngest age group, more than one-third of patients randomised to treatment with MDI switched to CSII, whereas only one patient (3%) switched from CSII to MDI. In the oldest age group, the converse was true, with more than twice as many participants switching from CSII to MDI; however, in the middle age group, switching between treatment arms was more balanced.

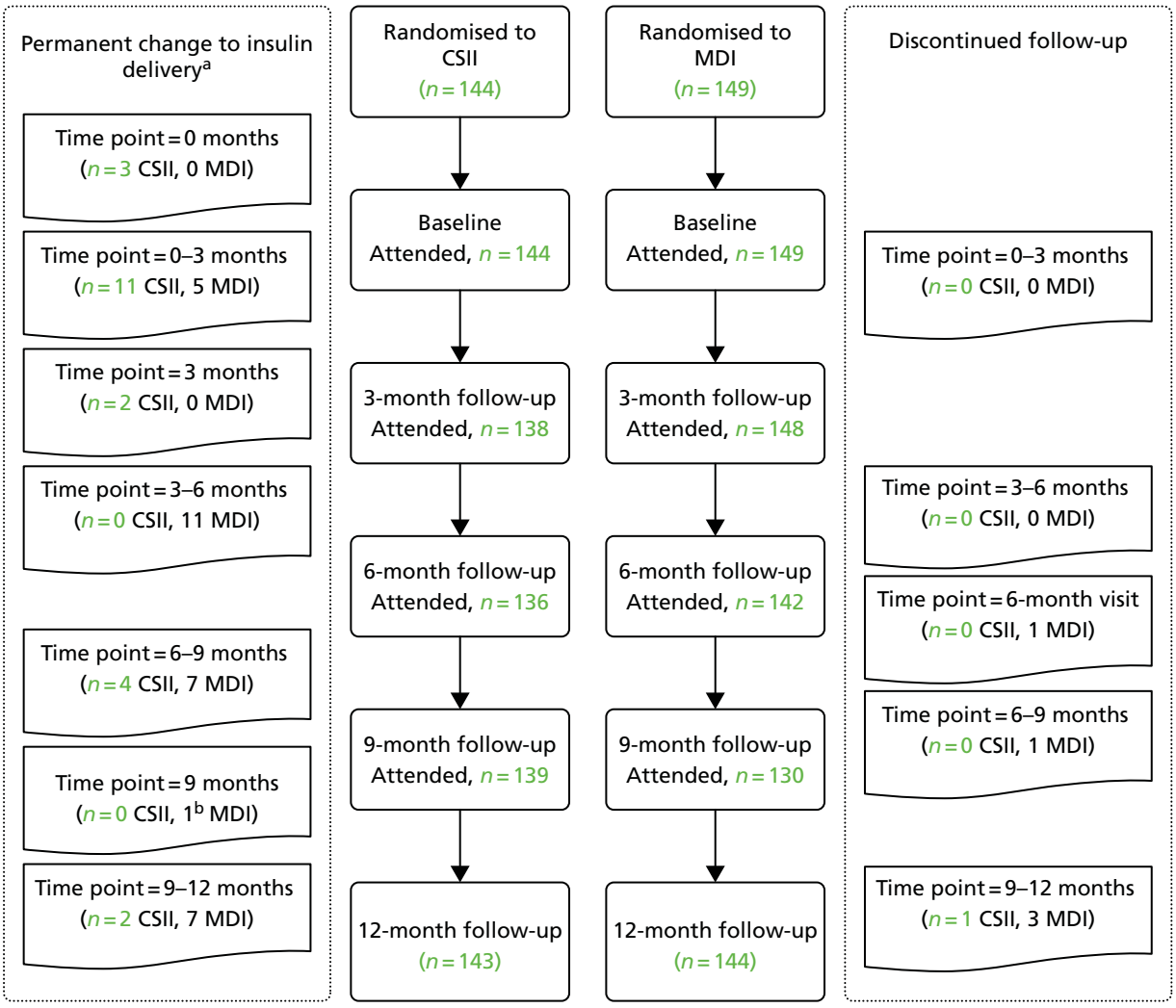

FIGURE 3 Retention and adherence. a, Permanent change of insulin delivery from randomised treatment but continuing follow-up; b, patient changed from MDI to injections ter die sumendus (TDS) regime.

TABLE 6 Permanent changes to insulin delivery by age and time point

	CSII to MDI							MDI to CSII					
		Time point (months)							Time point (months)				
Age (years)	*n*	0	0–3	3–6	6–9	9–12	Total (%)	*n*	0–3	3–6	6–9	9–12	Total (%)
< 5	33	1	0	0	0	0	1 (3.0)	32	3	4	2	3	12 (37.5)
5–11	71	2	5	0	2	1	10 (14.1)	76	1	5	4	4	14 (18.4)
≥ 12	40	0	6	2	2	1	11 (27.5)	41	1	2	1	0	4 (9.8)
Total	144	3	11	2	4	2	22 (15.3)	149	5	11	7	7	30 (20.1)

When movement between treatment arms was examined by study centre, we found two centres in which there was dominance for switch from MDI to CSII, with one centre switching four out of five patients from MDI to CSII and none from CSII to MDI. In another centre, 9 out of 16 patients randomised to MDI switched to CSII and 3 out of 14 patients randomised to CSII switched to MDI. In other centres, movement between treatment arms was more balanced (see *Appendix 2*, *Figure 12*).

Data were collected relating to the decision to switch treatment arms and a summary is displayed in *Table 7*, with more detailed data in *Appendix 2*, *Table 29*. The most frequently cited reasons for switching treatment arm were parent or patient preference. The majority of the participants moving from CSII to MDI had a last HbA_{1c} measurement above the NICE recommendations applicable at the time of the switch; however, a larger proportion of those moving from MDI to CSII had HbA_{1c} measurements within the NICE recommendations.[19]

TABLE 7 Decision-making for permanent change to insulin delivery[a]

		HbA_{1c} concentration higher than recommended guideline (*n*)	Decision-makers				
Age (years)	*N*		Parent	Patient	Clinician	Frequency	Reasons (frequency)
Permanent change from CSII to MDI							
< 5	1	1	✗			1	Parent preference ($n = 1$)
5–11	10	9		✗		4	Patient/parent preference ($n = 10$)
			✗			1	
			✗	✗		3	Poor concordance with treatment ($n = 1$)
			✗	✗	✗	1	
			✗		✗	1	Poor control, frequent hyperglycaemia ($n = 1$)
							Pain at cannula site ($n = 1$)
							Did not want pump ($n = 1$)
≥ 12	10	9		✗		2	Patient/parent preference ($n = 10$)
			✗	✗		4	
			✗	✗	✗	4	Poor concordance with treatment ($n = 1$)
				✗	✗	1	
							Poor control, frequent hyperglycaemia ($n = 1$)

TABLE 7 Decision-making for permanent change to insulin delivery[a] (*continued*)

Age (years)	*N*	HbA_{1c} concentration higher than recommended guideline (*n*)	Decision-makers				Reasons (frequency)
			Parent	Patient	Clinician	Frequency	
Permanent change from MDI to CSII							
< 5	12	10	✗			2	Age related (*n* = 2)
					✗	2	Patient/parent preference (*n* = 7)
			✗		✗	8	
							Poor control, frequent hyperglycaemia (*n* = 5)
							Bruising at injection site (*n* = 1)
5–11	14	5		✗		2	Patient/parent preference (*n* = 13)
			✗	✗		2	
			✗	✗	✗	9	Poor concordance with treatment (*n* = 2)
			✗		✗	1	
							Poor control, frequent hyperglycaemia (*n* = 1)
≥ 12	4	1		✗		1	Patient/parent preference (*n* = 4)
			✗	✗		1	
			✗	✗	✗	1	
				✗	✗	1	
Permanent change from MDI to injections TDS regime							
5–11	1	1	✗		✗	1	Patient/parent preference (*n* = 4)

a Not prespecified analysis in the statistical analysis plan.

Protocol deviations

Protocol deviations are summarised in *Table 8*. The most common major protocol deviation was the 12-month visit taking place outside the preferred time window. The median number of days outside the visit window was 2.0 [interquartile range (IQR) –5 to 10 days] and 2.5 (IQR –7 to 9.5 days) for the CSII and MDI arms, respectively.

Primary outcome: glycosylated haemoglobin measured at 12 months

Data on HbA_{1c} concentrations were available for 97% of participants (CSII, *n* = 143; MDI, *n* = 142).

The results for the primary outcome for the primary ITT analysis and the per-protocol analysis are provided in *Table 9*. The per-protocol analysis population excludes participants who had a major protocol deviation (see *Table 8*) or three or more minor deviations.

TABLE 8 Protocol deviations

Protocol deviations	Treatment arm, *n* (%)		Overall (*N* = 293), *n* (%)
	CSII (*N* = 144)	MDI (*N* = 149)	
Relating to inclusion and exclusion criteria	0 (0)	0 (0)	0 (0)
Relating to treatment and follow-up visits			
At least one major	57 (39.6)	77 (51.7)	134 (45.7)
Start of study treatment from diagnosis being > 10 days (protocol version 3.0)	1 (0.7)	1 (0.7)	2 (0.7)
Start of study treatment from diagnosis being > 14 days (protocol version 4.0)	1 (0.7)	3 (2)	4 (1.4)
Scheduled 12-month follow-up visit falling outside the ± 15-day window	36 (25)	49 (32.9)	85 (29)
Permanent change of insulin delivery	22 (15.3)	31[a] (20.8)	53[a] (18.1)
Usage of non-protocol-specified insulin[b]	10 (6.9)	13 (8.7)	23 (7.8)
At least one minor	70 (48.6)	87 (58.4)	157 (53.6)
At least three minor	0 (0)	0 (0)	0 (0)
Scheduled 3-month follow-up visit falling outside the ± 15-day window	34 (23.6)	44 (29.5)	78 (26.6)
Scheduled 6-month follow-up visit falling outside the ± 15-day window	43 (29.9)	48 (32.2)	91 (31.1)
Scheduled 9-month follow-up visit falling outside the ± 15-day window	44 (30.6)	39 (26.2)	83 (28.3)
At least one major and/or at least three minor	57 (39.6)	77 (51.7)	134 (45.7)

a One permanent switch of insulin delivery method was from MDI to 'injections TDS regime'.
b Does not include insulin detemir.
Of the 134 protocol deviations, two deviations took place in two participants (CSII, *n* = 1; MDI, *n* = 1) who withdrew prior to 12 months.

TABLE 9 Glycosylated haemoglobin levels measured at 12 months

HbA_{1c} concentration (mmol/mol) at 12 months	Treatment arm			Mean[a,b] (95% CI)		Mean[a] difference between treatment groups (CSII – MDI) (95% CI)	*p*-value
	CSII	MDI	Total	CSII	MDI		
Primary analysis: ITT analysis (age group)							
7 months to < 5 years							
n (missing)[c]	33 (0)	31 (1)	64 (1)	60.9 (58.5 to 63.3)	58.5 (56.1 to 60.9)	2.4 (–0.4 to 5.3)	0.09
Mean (SD)	63.9 (12.1)	58.4 (9.9)	61.2 (11.3)				
5 years to < 12 years							
n (missing)[c]	70 (1)	72 (4)	142 (5)				
Mean (SD)	58 (11.4)	59.3 (11.4)	58.7 (11.4)				
12 years to < 16 years							
n (missing)[c]	40 (0)	39 (2)	79 (2)				
Mean (SD)	61.3 (13.3)	54.7 (14.7)	58.1 (14.3)				

TABLE 9 Glycosylated haemoglobin levels measured at 12 months (*continued*)

HbA_{1c} concentration (mmol/mol) at 12 months	Treatment arm			Mean[a,b] (95% CI)		Mean[a] difference between treatment groups (CSII – MDI) (95% CI)	*p*-value
	CSII	MDI	Total	CSII	MDI		
Per-protocol analysis (age group)							
7 months to < 5 years							
n (missing)[d]	23 (10)	11 (21)	34 (31)	60.2 (56.4 to 63.9)	59.3 (55.3 to 63.3)	0.9 (–3.2 to 5)	0.67
Mean (SD)	62.6 (13.1)	56.2 (11)	60.5 (12.6)				
5 years to < 12 years							
n (missing)[d]	41 (30)	32 (44)	73 (74)				
Mean (SD)	57.9 (11.8)	59.7 (10.8)	58.7 (11.3)				
12 years to < 16 years							
n (missing)[d]	23 (17)	23 (18)	46 (35)				
Mean (SD)	57.6 (14.2)	57.8 (16.8)	57.7 (15.4)				

a Least mean squares.
b This was not prespecified in the statistical analysis plan but has been added to aid interpretation.
c There were missing values in the ITT analysis owing to five withdrawals prior to 12 months and one missing value.
d There were missing values in the per-protocol analysis owing to six withdrawals prior to 12 months, two with missing values, and 132 protocol deviations.

The HbA_{1c} measurement was marginally higher in the CSII group than in the MDI group (mean difference 2.4 mmol/mol; 95% CI –0.4 to 5.3 mmol/mol), although the observed difference was not statistically significant. This result was consistent when compared with the per-protocol analysis (see *Tables 4* and *5* for comparison of baseline characteristics of all randomised participants and *Appendix 2*, *Table 30*, for baseline characteristics of the per-protocol analysis population). A summary of the data sources (local or central laboratory) used in the primary ITT analysis and the per-protocol analysis is provided in *Table 10*.

TABLE 10 Data source of HbA_{1c} concentration measured at 12 months

Laboratory value used for primary outcome analysis	Analysis, *n* (%)			
	ITT		Per-protocol	
	CSII	MDI	CSII	MDI
Aged < 5 years				
Central	22 (66.7)	26 (83.9)	15 (65.2)	11 (100)
Local	11 (33.3)	5 (16.1)	8 (34.8)	–
Aged 5–11 years				
Central	58 (82.9)	58 (80.6)	34 (82.9)	27 (84.4)
Local	12 (17.1)	14 (19.4)	7 (17.1)	5 (15.6)
Aged ≥ 12 years				
Central	32 (80)	33 (84.6)	18 (78.3)	20 (87)
Local	8 (20)	6 (15.4)	5 (21.7)	3 (13)
Total				
Central	112 (77.8)	117 (78.5)	67 (77.0)	58 (87.9)
Local	31 (21.5)	25 (16.8)	20 (23.0)	8 (12.1)

Exploratory analyses including HbA_{1c} concentrations measured at baseline as a continuous explanatory variable in the age-adjusted model did not alter the SCIPI study conclusions for CSII compared with MDI at 12 months [least square mean difference between treatment groups (CSII – MDI) 2.9; 95% CI –0.02 to 5.9], but did suggest the importance of early baseline values for 12-month measurements (HbA_{1c} concentration baseline coefficient estimate 0.07; standard error 0.03; 95% CI 0.01 to 0.13).

An additional exploratory analysis considered the impact of the deprivation score by including it in the age strata-adjusted model and found that it did not alter conclusions [least square mean difference (CSII – MDI) 2.2; 95% CI –0.7 to 5.0]. The model suggested that higher deprivation score was associated with higher HbA_{1c} concentrations at 12 months (0.03, standard error 0.04, 95% CI –0.05 to 0.12).

Mean profile plots are provided for each age stratum in *Figure 4*. The results from including an age stratum by treatment group interaction with age as a main effect in the model are provided in *Table 11*. The least mean square estimates are 61.5 (95% CI 59.1 to 63.9) for CSII, 57.9 (95% CI 55.5 to 60.3) for MDI and 3.6 (95% CI 0.6 to 6.6) for the difference (CSII – MDI).

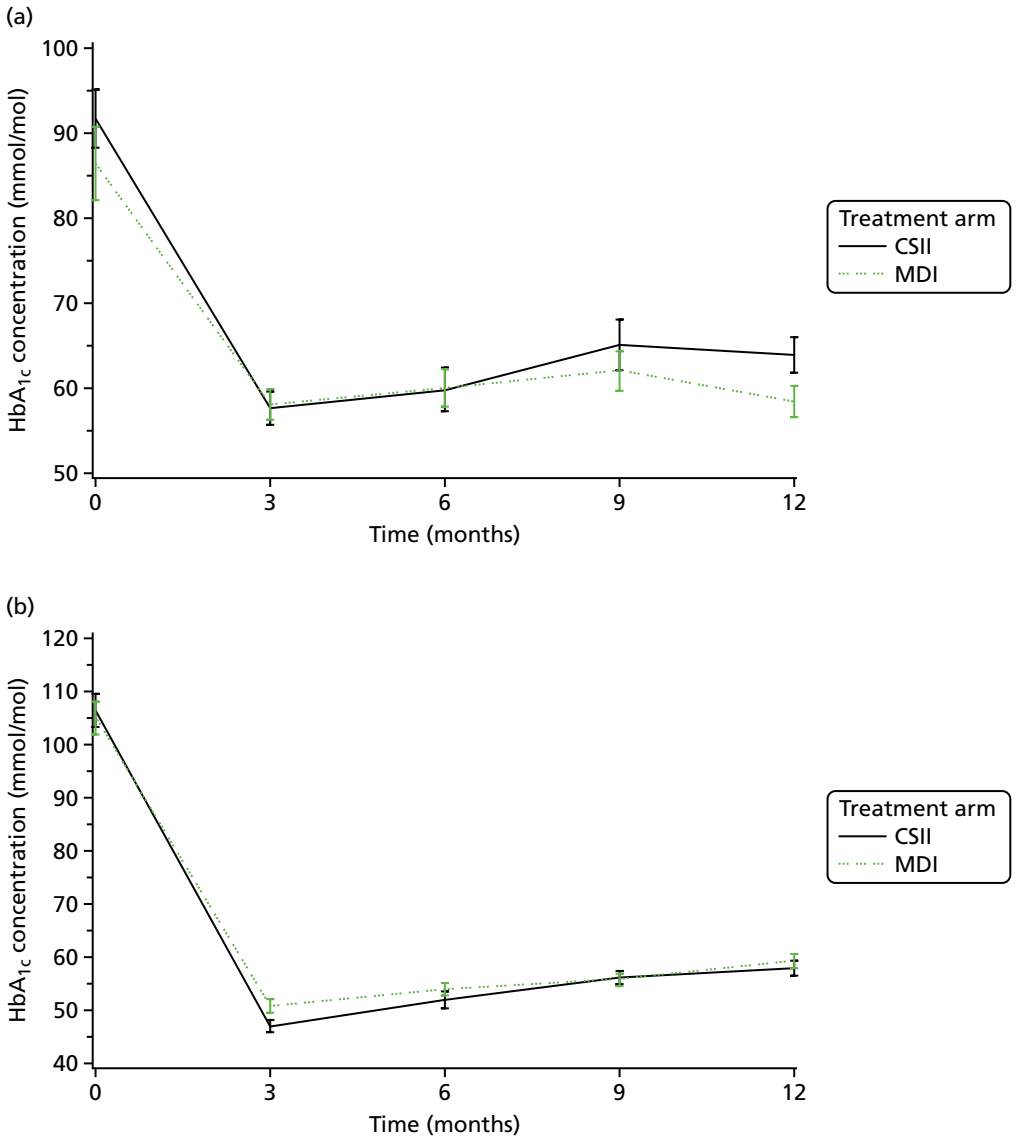

FIGURE 4 Glycosylated haemoglobin (mmol/mol) mean profile plots by age stratum. (a) Participants aged < 5 years; (b) participants aged 5–11 years; and (c) participants aged ≥ 12 years. Not a prespecified analysis in the statistical analysis plan. (*continued*)

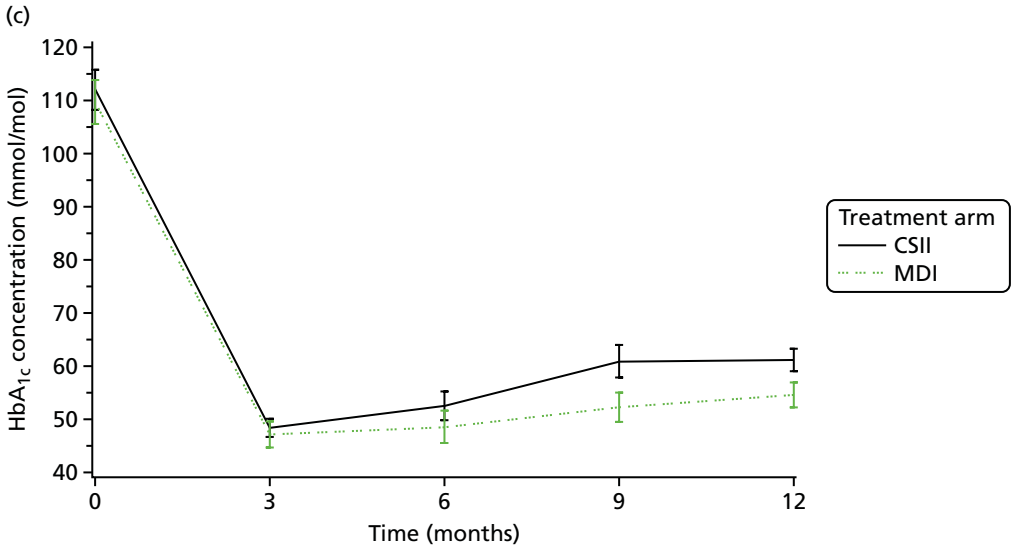

FIGURE 4 Glycosylated haemoglobin (mmol/mol) mean profile plots by age stratum. (a) Participants aged < 5 years; (b) participants aged 5–11 years; and (c) participants aged ≥ 12 years. Not a prespecified analysis in the statistical analysis plan.

TABLE 11 Exploratory analysis including treatment by age strata as a covariate

Effect (CSII – MDI)	Estimate[a]	Standard error	95% CI
Treatment × ≥ 12 years	6.5001	2.7026	1.1788 to 11.8213
Treatment × 5–11 years	–1.2540	2.0148	–5.2210 to 2.7130
Treatment × < 5 years	5.5902	3.0029	–0.3223 to 11.5027

a Not prespecified analysis in the statistical analysis plan.

Figure 5 displays the consistency of treatment effect across the SCIPI study centres. The consistency of treatment effect across sites is evident by the overlapping CIs. There is no statistical evidence for differences between sites from the chi-squared test for heterogeneity ($p = 0.51$) and I^2 (0%). *Figure 6* displays the treatment effect in 6-month periods to consider potential presence of a learning curve from the first randomisations. The period of 0–6 months includes the first 6 months of randomisations within each centre. The graph does not suggest a pattern of reducing treatment effect by time.

Secondary outcomes

The target HbA_{1c} value that was recommended by NICE[19] at the start of the SCIPI study was < 58 mmol/mol. In August 2015, this was revised to be < 48 mmol/mol. To reflect current practice, the secondary outcome that had previously been < 58 mmol/mol was changed in a protocol amendment (version 7.0). However, as the majority of the SCIPI study participants would have been randomised and followed up with diabetes teams aiming to attain HbA_{1c} values of < 58 mmol/mol, the results for both are presented in *Table 12*. Greater proportions of participants on the MDI arm attained values below the target thresholds; however, results are not statistically significant.

The incidences of severe hypoglycaemia and DKA were low, with only eight and two participants experiencing these events, respectively. Although participants on CSII had a greater event rate, for both events, the wide CIs reflect the low number of event rates and, hence, a high level of uncertainty.

Study or subgroup	CSII Mean	CSII SD	CSII Total	MDI Mean	MDI SD	MDI Total	Weight	Mean difference IV, fixed, 95% CI
00036 Norfolk and Norwich University Hospitals NHS	60.7555	11.9268604	4	49.25	8.0156098	4	3.7%	11.51 (–2.58 to 25.59)
00086 Doncaster Royal Infirmary	55.25	10.9642275	8	59.6666667	11.6404467	9	6.3%	–4.42 (–15.17 to 6.33)
00104 Stafford Hospital	0	0	0	57	4.2426407	2		Not estimable
00114 Southampton University Hospitals NHS Trust	64.2142857	15.5324899	14	61.1333333	13.0376743	15	6.6%	3.08 (–7.39 to 13.56)
00133 Birmingham Children's Hospital	61.5	13.541183	12	59.5555556	11.7910041	9	6.2%	1.94 (–8.92 to 12.81)
00148 Ipswich Hospital	56.6666667	8.3864971	3	48.3333333	4.7258156	3	6.1%	8.33 (–2.56 to 19.23)
00160 Royal Preston Hospital	0	0	0	67.5	7.7781746	2		Not estimable
00213 Nottingham University Hospital NHS Trust	57.7741935	11.1376529	31	55.8666667	13.6879845	30	18.5%	1.91 (–4.37 to 8.18)
00243 Alder Hey Children's NHS Foundation Trust	58.6923077	11.3517196	26	55.1666667	12.7370281	24	16.2%	3.53 (–3.18 to 10.23)
00248 Sheffield Children's NHS Foundation Trust	64	13.2916014	4	52.6666667	10.7857931	3	2.3%	11.33 (–6.52 to 29.18)
00326 East Surrey Hospital	61.2	4.5077711	3	69.25	10.8435849	4	5.2%	–8.05 (–19.84 to 3.74)
01527 Royal Blackburn Hospital	61.07983	12.6936387	5	61.6666667	11.2368442	6	3.6%	–0.59 (–14.89 to 13.72)
04913 Cardiff and Vale University Local Health Board	59.3333333	9.8361578	9	61.5555556	9.0015431	9	9.6%	–2.22 (–10.93 to 6.49)
05042 Oxford Radcliffe Hospitals NHS Trust	62.3333333	15.8336945	18	54.7647059	10.9231944	17	9.0%	7.57 (–1.40 to 16.54)
12617 The Newcastle upon Tyne Hospitals NHS	68.3333333	8.2623645	6	68.8	9.2032603	5	6.7%	–0.47 (–10.90 to 9.96)
Total (95% CI)			143			142	100.0%	2.16 (–0.54 to 4.86)

Heterogeneity: $\chi^2 = 11.21$, df = 12 ($p = 0.51$); $I^2 = 0\%$
Test for overall effect: $z = 1.57$ ($p = 0.12$)

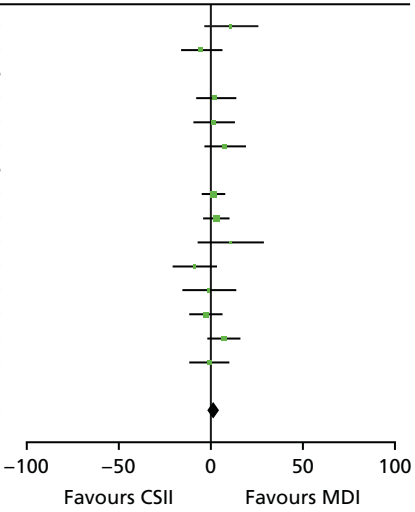

FIGURE 5 Forest plot of HbA_{1c} concentrations at 12 months by site. IV, inverse variance.

Study or subgroup	CSII Mean	CSII SD	CSII Total	MDI Mean	MDI SD	MDI Total	Mean difference IV, fixed, 95% CI
01: 0–0.5 years	59.83125	11.24944264	32	58.17142857	12.02078033	35	1.66 (–3.91 to 7.23)
02: 0.5–1 year	61	9.6695398	25	57.23809524	11.28230811	21	3.76 (–2.37 to 9.90)
03: 1–1.5 years	59.80686724	14.08933527	29	64.39130435	13.56043419	23	–4.58 (–12.13 to 2.97)
04: 1.5–2 years	61.09090909	12.89115271	22	52.82142857	8.80678851	28	8.27 (1.97 to 14.57)
05: 2–2.5 years	56.38461538	11.14703594	13	55	11.54700538	16	1.38 (–6.91 to 9.67)
06: 2.5–3 years	61.625	16.69281282	16	60.61538462	14.76221789	13	1.01 (–10.45 to 12.47)
07: 3–3.5 years	64	4.24264069	2	56.5	6.8556546	4	7.50 (–1.43 to 16.43)
08: 3.5–4 years	63.75	6.39661369	4	61.5	26.1629509	2	2.25 (–34.55 to 39.05)

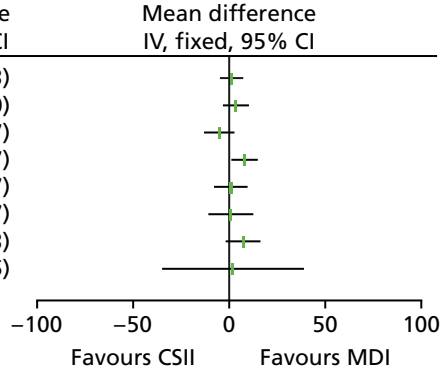

FIGURE 6 Forest plot to consider treatment effect learning curve. Not prespecified analysis in the statistical analysis plan. IV, inverse variance.

TABLE 12 Secondary outcomes: target HbA_{1c} concentration, severe hypoglycaemia, DKA and partial remission

Target HbA_{1c} concentration	Treatment arm, *n* (%)		Overall (*N* = 293), *n* (%)	Relative risk (95% CI)	*p*-value[a]
	CSII (*N* = 144)	MDI (*N* = 149)			
< 48 mmol/mol	22 (15.4)	29 (20.4)	51 (17.9)	0.75 (0.46 to 1.25)	0.28
Missing	1	5			
< 58 mmol/mol	66 (46.2)	78 (54.9)	144 (50.5)	0.84 (0.67 to 1.06)	0.16
Missing	1	5			
Severe hypoglycaemia[b]	6 (4.2)	2 (1.3)	8 (2.7)	3.1 (0.6 to 15.1)	0.17
Missing	10	0			
DKA	2 (1.4)	0	2 (0.7)	5.2 (0.3 to 106.8)	0.24
Missing	10	0			
Partial remission	21 (24.4)	21 (32.8)	42 (28.0)	0.74 (0.45 to 1.24)	0.28
Missing	58	85			

a Chi-squared test.
b The statistical analysis plan says 'Severe hypoglycaemia is a *type of related AE* . . . Cases of hypoglycaemia mild or moderate in *severity* are not counted as events for this analysis'. 'Severe hypoglycaemia' is the *type* of AE and this terminology is used in general clinical practice regardless of AE *severity* so it is, thus, possible to have a moderate or mild 'severe hypoglycaemia'. Prior to the final analysis being undertaken all cases of 'severe hypoglycaemia' were queried with the site again to double-check whether or not it was happy with the AE type and severity.

A higher proportion of participants randomised to MDI were in partial remission at 12 months. However, levels of missing data were high for this outcome because of the lack of availability of the daily insulin dose data required to calculate its occurrence. The formula used to calculate partial remission is available in the statistical analysis plan, which is available on the National Institute for Health Research website (www.journalslibrary.nihr.ac.uk/programmes/hta/081439/#/; accessed 13 February 2018).

There was no significant difference in change in BMI SDS or height SDS between those randomised to CSII and those randomised to MDI (*Table 13*). Insulin requirements were significantly lower for those randomised to MDI than for those randomised to CSII (see *Table 13*). Similarly, with partial remission, the low availability of dose data increased levels of missing data. Owing to the availability of CSII data, levels of missing data are higher in the MDI arm.

Quality of life

Tables 14 and *15* present results for QoL as measured by the PedsQL instruments for parents and children, respectively, stratified by instrument age category. Results for each domain are available in *Appendix 2*, *Tables 31* and *32*.

In parent-reported QoL, there was a tendency for parents with children randomised to CSII to report higher QoL scores than those on MDI. This was consistent across instrument age strata, the 6- and 12-month follow-up time points and the child-reported scores. Estimates of the least mean squares difference between treatment groups (CSII – MDI) were 4.1 (95% CI 0.6 to 7.6; $p = 0.02$) for parent-reported and 3.1 (95% CI –0.6 to 6.8; $p = 0.1$) for child-reported QoL. It should be noted, however, that child-reported QoL starts from age 5 years but the parent-reported QoL starts from age 2 years and that, in general, the size of the differences and CI widths are similar.

TABLE 13 Secondary outcomes: change in BMI SDS, change in height SDS and insulin requirements

Summary	Treatment arm		Total	CSII – MDI[a] (95% CI)	*p*-value
	CSII	MDI			
Change in BMI SDS					
7 months to < 5 years					
n (missing)	124 (20)	132 (17)	256 (37)	0.1 (0 to 0.3)	0.13
Mean (SD)	0.2 (1.3)	0.1 (1.3)	0.1 (1.3)		
Median (IQR)	0.2 (–0.7 to 0.9)	0.1 (–0.8 to 1)	0.2 (–0.8 to 1)		
Minimum, maximum	–2.9, 4.2	–4, 3.5	–4, 4.2		
5 years to < 12 years					
n[a] (missing)	142 (1)	138 (6)	280 (7)		
Mean (SD)	0.8 (1.1)	0.7 (1)	0.7 (1.1)		
Median (IQR)	0.8 (0.1 to 1.5)	0.6 (0 to 1.4)	0.6 (0 to 1.4)		
Minimum, maximum	–1.8, 4.1	–2.7, 3	–2.7, 4.1		
12 years to < 16 years					
n[a] (missing)	122 (21)	122 (22)	244 (43)		
Mean (SD)	0.6 (0.8)	0.5 (0.8)	0.5 (0.8)		
Median (IQR)	0.5 (0.1 to 1)	0.4 (–0.1 to 0.9)	0.5 (0 to 0.9)		
Minimum, maximum	–1.4, 3.4	–1.1, 5.3	–1.4, 5.3		
Change in height SDS					
7 months to < 5 years					
n (missing)	124 (20)	132 (17)	256 (37)	–0.1 (–0.2 to 0)	0.10
Mean (SD)	0.3 (1.1)	0.3 (1)	0.3 (1)		
Median (IQR)	0.1 (–0.4 to 1.1)	0.4 (–0.3 to 1.1)	0.3 (–0.3 to 1.1)		
Minimum, maximum	–2.3, 3.3	–2.9, 2.4	–2.9, 3.3		
5 years to < 12 years					
n[a] (missing)	142 (2)	138 (11)	280 (13)		
Mean (SD)	0.2 (1.1)	0.3 (1)	0.3 (1)		
Median (IQR)	0.1 (–0.6 to 1)	0.3 (–0.3 to 1)	0.2 (–0.5 to 1)		
Minimum, maximum	–2.1, 3.5	–2.7, 2.3	–2.7, 3.5		
12 years to < 16 years					
n[a] (missing)	122 (22)	122 (27)	244 (49)		
Mean (SD)	–0.1 (0.5)	0 (0.4)	0 (0.4)		
Median (IQR)	0 (–0.2 to 0.2)	0 (–0.2 to 0.2)	0 (–0.2 to 0.2)		
Minimum, maximum	–2.8, 0.7	–1.7, 1.6	–2.8, 1.6		
Insulin requirements (unit/kg/day)					
7 months to < 5 years					
n (missing)	24 (9)	13 (19)	37 (28)	0.1 (0.0 to 0.2)	0.01
Mean (SD)	0.7 (0.2)	0.7 (0.1)	0.7 (0.2)		
Median (IQR)	0.8 (0.6 to 0.8)	0.6 (0.6 to 0.7)	0.7 (0.6 to 0.8)		
Minimum, maximum	0.3, 1.2	0.4, 0.9	0.3, 1.2		

TABLE 13 Secondary outcomes: change in BMI SDS, change in height SDS and insulin requirements (*continued*)

Summary	Treatment arm		Total	CSII – MDI[a] (95% CI)	*p*-value
	CSII	MDI			
5 years to < 12 years					
n (missing)	45 (26)	38 (38)	83 (64)		
Mean (SD)	0.6 (0.2)	0.6 (0.3)	0.6 (0.3)		
Median (IQR)	0.6 (0.5 to 0.8)	0.6 (0.4 to 0.7)	0.6 (0.4 to 0.8)		
Minimum, maximum	0.2, 1.2	0, 1.2	0, 1.2		
12 years to < 16 years					
n (missing)	18 (22)	13 (28)	31 (50)		
Mean (SD)	0.8 (0.2)	0.5 (0.4)	0.7 (0.3)		
Median (IQR)	0.8 (0.6 to 0.9)	0.7 (0 to 0.8)	0.7 (0.5 to 0.9)		
Minimum, maximum	0.4, 1.2	0, 0.9	0, 1.2		

a Adjusted mean difference, adjusted for age group and centre as random effects.

TABLE 14 Overall PedsQL parent-reported scores

Summary	Time point					
	6 months[a]			12 months		
	CSII	MDI	Total	CSII	MDI	Total
Parents/carers of 2- to 4-year-old children						
n	24	18	42	20	17	37
Median (IQR)	72.8 (62.9–77.2)	61.8 (55.5–74.1)	68.8 (57–76.8)	75 (62.1–82.1)	70.5 (54.7–79.5)	73.2 (60.7–80.4)
Minimum, maximum	54.5, 98.6	46.7, 81.6	46.7, 98.6	52.4, 99.1	40.2, 90.2	40.2, 99.1
Parents/carers of 5- to 7-year-old children						
n	13	23	36	16	17	33
Median (IQR)	70.5 (63.5–85.7)	69.6 (65.2–80.4)	69.8 (65.1–80.8)	75.6 (60.4–86.6)	72.3 (64.7–76)	73.2 (63.4–81.3)
Minimum, maximum	51.8, 90.2	54.7, 84.4	51.8, 90.2	45.5, 94.6	49.1, 86.6	45.5, 94.6
Parents/carers of 8- to 12-year-old children						
n	58	56	114	54	55	109
Median (IQR)	73.2 (65.2–84.2)	68.8 (63.4–78.8)	70.5 (64.3–81.5)	74.5 (65.9–81.3)	67.9 (57.1–77.7)	70.5 (61.6–80.4)
Minimum, maximum	31.3, 94.6	34.8, 95.8	31.3, 95.8	39.5, 100	34.2, 99.1	34.2, 100
Parents/carers of 13- to 16-year-old children						
n	29	28	57	38	34	72
Median (IQR)	73.2 (59.8–84.3)	67.6 (55.6–74.9)	69.6 (58.9–80.4)	67.3 (58–80.7)	67.4 (59.8–79.5)	67.3 (58.9–80.1)
Minimum, maximum	42, 99.1	35.1, 98.2	35.1, 99.1	41.1, 96.4	19.6, 91.1	19.6, 96.4

a Not prespecified in the statistical analysis plan to present data at 6 months.

TABLE 15 Overall PedsQL child-reported scores[a]

Summary	Time point					
	6 months			12 months		
	CSII	MDI	Total	CSII	MDI	Total
5- to 7-year-old children						
n	11	21	32	13	18	31
Median (IQR)	75 (51.5–80.4)	70.9 (67.9–80.4)	71.4 (67–80.4)	78.6 (60.7–85.7)	76.4 (60.7–81.6)	76.8 (60.7–82.1)
Minimum, maximum	41.1, 83.4	55.4, 87.5	41.1, 87.5	39.3, 89.3	30.4, 85.7	30.4, 89.3
8- to 12-year-old children						
n	58	54	112	54	53	107
Median (IQR)	79.1 (66.6–84.8)	71.5 (64.3–80.4)	75.9 (66.3–83.6)	81.7 (70.7–88.4)	76.8 (64.3–85.7)	77.7 (70.5–87.8)
Minimum, maximum	45.5, 94.1	40.2, 99.1	40.2, 99.1	44.6, 100	39.8, 96.4	39.8, 100
13- to 16-year-old children						
n	29	29	58	37	33	70
Median (IQR)	79.5 (71.4–87.6)	75.9 (67–82.1)	76.9 (69.6–85.7)	75 (63.4–84.8)	73.2 (60.7–79.3)	74.7 (60.7–84.8)
Minimum, maximum	43.8, 99.1	50, 98.2	43.8, 99.1	47.3, 95.5	35.7, 94.6	35.7, 95.5

a Not prespecified in the statistical analysis plan to present data at 6 months.

Safety analysis

Table 12 reports on incidences of hypoglycaemia and DKA in the ITT analysis population. In this section, the data set contains all participants who were randomised and received at least one dose of trial medication. For AEs, the method of insulin delivery that the participants were receiving at the time of AE onset was used, rather that the allocated treatment, to take into account that participants could temporarily or permanently switch treatment. The total number of events experienced and the number of participants experiencing at least one event are provided along with the IDR (the number of patients with at least one new AE per population at risk in a given time period):

- The incidence of related AEs by treatment group was 54 in 36 patients who were on CSII at the time of the AE. IDR was 25.0 patients with at least one event per 100 person-years and 17 AEs in 16 patients who were on MDI at the time of the AE. IDR was 10.5 patients with at least one event per 100 person-years.
- The incidence of related SAEs by treatment group was 14 SAEs in nine patients who were on CSII at the time of the SAE. IDR was 6.2 patients with at least one event per 100 person-years and eight SAEs in eight patients who were on MDI at the time of the SAE. IDR was 5.3 patients with at least one event per 100 person-years.

Tables 16 and *17* provide the summary of related AEs and SAEs, respectively.

TABLE 16 Summary of related AEs

Description	Treatment arm					
	CSII (144.1 total person-years, *N* = 144 patients)		MDI (151.9 total person-years, *N* = 149 patients)		Total (296.1 total person-years, *N* = 293 patients)	
	Events (*n*)	Patients, *n* (IDR)	Events (*n*)	Patients, *n* (IDR)	Events (*n*)	Patients, *n* (IDR)
All						
DKA	2	2 (1.4)	0	0 (0)	2	2 (0.7)
Insulin administration error	2	2 (1.4)	5	5 (3.3)	7	6 (2)
Pump failure	4	3 (2.1)	0	0 (0)	4	3 (1)
Severe hypoglycaemia	6	6 (4.2)	2	2 (1.3)	8	8 (2.7)
Site infections	8	7 (4.9)	0	0 (0)	8	7 (2.4)
Other – specify	32	22 (15.3)	10	10 (6.6)	42	32 (10.8)
Device						
DKA	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Pump failure	4	3 (2.1)	0	0 (0)	4	3 (1)
Severe hypoglycaemia	2	2 (1.4)	0	0 (0)	2	2 (0.7)
Site infections	8	7 (4.9)	0	0 (0)	8	7 (2.4)
Other – specify	14	11 (7.6)	3	3 (2)	17	14 (4.7)
Carer error						
Insulin administration error	1	1 (0.7)	4	4 (2.6)	5	5 (1.7)
Other – specify	5	2 (1.4)	0	0 (0)	5	2 (0.7)
Meter error						
Other – specify	3	3 (2.1)	1	1 (0.7)	4	4 (1.4)
Incidental illness						
Insulin administration error	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Other – specify	5	5 (3.5)	3	3 (2)	8	8 (2.7)
Other						
DKA	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Insulin administration error	0	0 (0)	1	1 (0.7)	1	1 (0.3)
Severe hypoglycaemia	4	4 (2.8)	2	2 (1.3)	6	6 (2)
Other – specify	5	4 (2.8)	3	3 (2)	8	7 (2.4)

TABLE 17 Summary of related SAEs

Description	Treatment arm					
	CSII (144.1 total person-years, *N* = 144 patients)		MDI (151.9 total person-years, *N* = 149 patients)		Total (296.1 total person-years, *N* = 293 patients)	
	Events (*n*)	Patients, *n* (IDR)	Events (*n*)	Patients, *n* (IDR)	Events (*n*)	Patients, *n* (IDR)
All						
DKA	2	2 (1.4)	0	0 (0)	2	2 (0.7)
Insulin administration error	2	2 (1.4)	3	3 (2)	5	4 (1.4)
Pump failure	0	0 (0)	0	0 (0)	0	0 (0)
Severe hypoglycaemia	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Site infections	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Other – specify	8	6 (4.2)	5	5 (3.3)	13	11 (3.7)
Device						
DKA	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Pump failure	0	0 (0)	0	0 (0)	0	0 (0)
Severe hypoglycaemia	0	0 (0)	0	0 (0)	0	0 (0)
Site infections	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Other – specify	0	0 (0)	0	0 (0)	0	0 (0)
Carer error						
Insulin administration error	1	1 (0.7)	2	2 (1.3)	3	3 (1)
Other – specify	0	0 (0)	0	0 (0)	0	0 (0)
Meter error						
Other – specify	0	0 (0)	0	0 (0)	0	0 (0)
Incidental illness						
Insulin administration error	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Other – specify	5	4 (2.8)	2	2 (1.3)	7	6 (2)
Other						
DKA	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Insulin administration error	0	0 (0)	1	1 (0.7)	1	1 (0.3)
Severe hypoglycaemia	1	1 (0.7)	0	0 (0)	1	1 (0.3)
Other – specify	3	2 (1.4)	3	3 (2)	6	5 (1.7)

Chapter 4 Economic evaluation

Introduction

Economic evaluations

Economic evaluations of CSII versus MDI have been reviewed by Cummins *et al.*[103] and, more recently, by Roze *et al.*,[104] Pozzilli *et al.*[105] and ourselves using targeted searches of the PubMed, Web of Science, Scopus, Cumulative Index to Nursing and Allied Health Literature, ProQuest and Cochrane databases. In total, 10 fully reported economic evaluations were identified.[62,81,103,106–112] Most are limited in their transferability to the paediatric setting, as they relate to adult populations, and only two evaluations consider children and adolescent populations.[106,107]

Cohen *et al.*[106] examined the cost-effectiveness of CSII with MDI in adults and in children/young adults with T1D from the perspective of the Australian single-payer health-care system. They applied the Center for Outcomes Research (CORE) diabetes model (CDM) to simulate the lifetime progression of diabetes in adolescent patients with the following baseline characteristics: a mean age of 17.1 years, a mean duration of diabetes of 6.3 years and a mean HbA_{1c} concentration of 8.9%.[113,114]

The effectiveness of CSII in the base-case analysis was based on the results of a meta-analysis of 52 studies that included 1500 patients of all ages.[115] Compared with MDI, the meta-analysis suggested that treatment with CSII for ≥ 1 year was associated with a mean decrease in baseline HbA_{1c} concentration of 1.2%. The base-case analysis assumed no differences between interventions in the frequency of hypoglycaemic events. Annual costs of CSII and MDI were based on pump costs (and assumed an 8-year pump life), insulin costs, consumables, self-monitoring of blood glucose and medical professional assistance with pump initiation, maintenance and operation. The costs of managing complications and health state utilities were taken from published sources. All costs and outcomes were discounted at an annual rate of 5%.

The results indicated gains in discounted quality-adjusted life-years (QALYs) of 0.560 and a cost increase of AU$41,779 in CSII compared with MDI. The incremental cost per QALY gained was AU$74,661, which is marginally cost-effective at the Australian threshold for cost-effectiveness. This was sensitive to change in HbA_{1c} concentration: a reduction to 0.51% for CSII versus MDI increased the incremental cost-effectiveness ratio (ICER) to AU$114,818. Reducing the effective lifespan of the insulin pump from 8 to 6 years increased the ICER by 11%.

St Charles *et al.*[107] modelled the cost-effectiveness of CSII in T1D populations, including children and young adults, based on a third-party US payer perspective. Patients' baseline demographics, risk factors and pre-existing complications were taken from Doyle *et al.*[35] and the Diabetes Control Complications Trial Research Group secondary intervention cohort,[3] with a mean age of 13.0 years (range 8–21 years), a mean duration of diabetes of 5.6 years and a mean HbA_{1c} concentration of 8.2%.

For their base-case analysis, the authors assigned a greater reduction in HbA_{1c} concentration to CSII (0.9%) than to MDI (0.1%), based on a 16-week randomised trial of 32 children and young adults with T1D.[35] They further assumed an insulin pump lifetime of 7 years and 50% lower hypoglycaemia event rates in CSII based on an observational study[116] and reviews of outpatient insulin therapy in T1D patients.[117–119] Costs and outcomes were extrapolated over a lifetime using the CDM and discounted at a rate of 3% per annum.

The base-case ICER, of US$27,195 per QALY gained, was sensitive to (1) the lifespan of the pump, rising to US$40,652 per QALY gained for a 4-year lifetime, (2) the HbA_{1c} concentration improvement with CSII, rising to US$37,326 per QALY gained with a reduction in HbA_{1c} concentration of 0.675%, and (3) the hypoglycaemia event rate, with the ICER increasing to US$45,595 per QALY gained and no improvement

in CSII over MDI. The model was less sensitive to changes in the discount rate. The higher treatment costs associated with CSII in comparison with MDI (US$37,636 over a lifetime) were more than twice the expected savings from fewer complications (US$16,172).

An important limitation of both studies[106,107] was that they modelled the costs and consequences of CSII and MDI using data from disparate sources. They relied on small studies for the estimated improvement in HbA_{1c} concentration and made assumptions relating to the frequency of hypoglycaemic events and lifetime rates of T1D-related complications. The modelled outputs were very sensitive to these assumptions. Other long-term issues, including adherence and patient preference, could also potentially influence the cost-effectiveness of CSII, and although the CDM is a widely validated[120] and widely accepted[103] model in adult diabetes, there is no supporting evidence of validity in paediatric populations.[19]

Aim

The aim of the economic evaluation of the SCIPI study was to estimate the cost–utility, based on an assessment of the incremental costs per QALY gained, of treating paediatric T1D patients with CSII versus MDI. The costing perspective was that of the NHS in England. Within-trial QALYs were derived from patients', parents' or guardians' responses to the HUI Quetionnaire using the HU12 algorithm. Costs were derived by measuring health-care resource use associated with both CSII and MDI, including (1) purchase of pumps and pen devices, (2) consumables, (3) management of AEs, (4) procedures, (5) insulin, (6) hospitalisations and (7) contact with health-care professionals including GPs, school nurses, as an outpatient and at the accident and emergency (A&E) department. Differences between intervention groups in the primary outcome would indicate the need for a lifetime extrapolation using the CDM, otherwise a 12-month time horizon would be adopted.

Methods

Resource use

The perspective of the analysis was that of the NHS in England, with the expectation the major cost drivers would be devices and consumables, such as cartridge sets, batteries and infusion sets for CSII, insulin use, glucose self-monitoring and outpatient visits.[104,106] Other potential high-cost resource usages were considered, including A&E department attendance, hospital inpatient stays (including intensive care units) and all contacts with health-care professionals, including GPs, hospital doctors, school nurses and other specialists in person, and by telephone, fax, text or e-mail.

The measurement of resource use required complementary approaches using data collected as part of the trial and as part of routine care. Patients' use of health-care services was obtained from:

1. Electronic patient-linked information costing system (PLICS) data and/or patient administration system (PAS) data of participating hospitals – PLICS and PAS data were used as a primary source for identifying inpatient stays and use of a paediatric intensive care unit (PICU) or high-dependency unit (HDU).
2. Baseline forms – RNs completed the relevant sections of the baseline forms to identify the devices that were assigned to SCIPI study patients [Medtronic pump, F. Hoffman-La Roche AG pump, MDI, F. Hoffman-La Roche AG Expert glucometer, Contour® Glucometer (Ascensia Diabetes Care, Newbury, UK)]. The baseline forms also recorded patients' self-reported contact with hospital services and health-care professionals in the 3 months prior to randomisation. When the patient was unsure of this, RNs contacted the patient's GP or referred to the patient's hospital notes. These forms were the primary source of baseline resource used.
3. Three-monthly patient questionnaires – RNs completed the relevant sections of the patient questionnaires in face-to-face interviews with trial participants, their parents or guardians to identify overnight hospital stays, number of nights, reason for admission and type of ward. Another section of the patient questionnaire was used to identify contacts with health-care professionals including GPs, consultants, non-consultant grade medical doctors, nurses, dietitians, psychologists, infusion specialists,

social workers as well as the places or means of contact: A&E department, outpatient, general practice, school visits, home visits telephone, fax, text and e-mail. When the patient was unsure, RNs contacted the patient's GP or referred to the patient's hospital notes. Patient questionnaires were used as a primary source of data for treatment as an outpatient, in an A&E department, by a GP or by other health-care professional contacts. They were used as a secondary source of data for inpatient, PICU or HDU stays, which was especially relevant if the patients had attended a different hospital for treatment.

4. Adverse event or SAE forms – RNs completed AE and SAE forms when trial participants were admitted to hospital with severe hypoglycaemia, DKA, site infections, pump failures, insulin administration errors or other diabetes and device-related causes. This information was used as a secondary source of data for inpatient stays and use of PICU or HDU stays, especially relevant if the patients had attended a different hospital for treatment.
5. Insulin prescription forms – insulin prescription forms were used as a primary source of insulin usage, as these are more likely to reflect the quantity of insulin dispensed and, therefore, the true cost of insulin. RNs contacted GPs and hospital personnel at 3-monthly intervals to record the number of boxes or vials of insulin prescribed to patients, along with the dates and insulin type. Each box contained five × 300-unit cartridges or five × 300-unit pens and each vial contained 1000 units. For young children, GPs occasionally prescribe two or three cartridges or pens; however, no part-boxes were reported in the case report form (CRF) and no assumptions were made based on patient age.
6. Three-monthly insulin usage forms – RNs documented patient usage of insulin in the 4 weeks prior to each 3-monthly visit through face-to-face interviews with trial participants, their parents and/or guardians. These data were used if their projected 12-month insulin usage exceeded the usage implied in the insulin prescription form.
7. Electronic pump download data – RNs downloaded insulin usage data from the patient insulin pumps and these were entered into an electronic database. These data were used if the 12-month insulin usage exceeded the usage implied in the insulin prescription and/or insulin usage forms.

Unit costs

All resource use was valued in monetary terms using appropriate unit costs estimated at the time of analysis (cost year was 2016). Healthcare Resource Group (HRG) codes were used as the main currency of the economic analysis for inpatient stays and were obtained directly from electronic PLICS/PAS data or assigned based on the description of the condition and complications when recorded in the patient questionnaire, AE or SAE forms. HRG codes have the advantage of most closely reflecting actual payments, with cost codes being allocated based on the latest available national tariff[121] (these being bundled care packages, reimbursed at a national level according to the NHS Payment by Results scheme; *Table 18*). The scheduled 3-monthly visits were also costed using the national tariff because these formed part of the ongoing multidisciplinary team integrated package of care approach recommended by NICE[19] and were not costed elsewhere. Unbundled care packages reimbursed at a local level, such as PICU and HDU stays, were costed using the latest available National Schedule costs.[122] Standard sources were used for the unit costs of all other primary health-care, A&E and outpatient contacts,[123] with consultation time estimated by discussing with 15 RNs representing all recruiting sites (*Table 19*). The costs of needles, test strips and insulin were based on those detailed in the *British National Formulary*[124] and the costs of pumps and estimated annual consumables were obtained from the suppliers (F. Hoffman-La Roche AG and Medtronic) (*Tables 20* and *21*). For the base-case analysis, insulin pump costs were divided by four to represent a 4-year lifetime and, for MDI patients, two refillable pens (1 × basal and 1 × bolus) were factored in at an estimate of £40 each per year.

Cost analysis

All hospital stays recoded in patient questionnaires and the baseline form were costed irrespective of whether or not they were related to diabetes. Bundled national tariff costs were based on the hospital spell and incorporated excess ward days and whether the case was elective or emergency.[125] Tariff codes were obtained primarily from PLICS and PAS data supplied by the participating hospitals but, if unavailable, were referenced to the associated form (AE, SAE, baseline or patient questionnaire) and an appropriate HRG code was assigned based on reason for admission, condition and any complications. Locally negotiated unbundled costs were similarly identified and costs were assigned directly from the National Schedule.

TABLE 18 Inpatient costs for the main HRGs

HRG code	HRG name	Elective		Non-elective		Costs for excess days (£ per day)
		Cost (£)	Trim-point (days)	Cost (£)	Trim-point (days)	
BZ01Z	Enhanced cataract surgery	982	5	1944	12	242
CZ05T	Tonsillectomy, 18 years and under without CC	1083	5	1013	5	330
FZ20E	Appendicectomy procedures, 18 years and under without major CC	2403	5	2379	5	268
FZ24E	Major therapeutic endoscopic upper or lower GI tract procedures, between 2 and 18 years	1366	5	1177	5	268
FZ62Z[a]	Endoscopic or intermediate upper GI tract procedures, between 2 and 18 years	864	5	893	5	268
FZ63Z	Combined upper and lower GI tract diagnostic endoscopic procedures	513	5	694	5	209
HA73B	Minor elbow and lower arm procedures for trauma, 18 years and under	1192	5	1192	5	317
PA03B	Febrile convulsions, 1 year and over	659	5	584	5	288
PA04A	Headaches and migraines, with CC	883	5	697	5	288
PA04B	Headaches and migraines, without CC	673	5	550	5	288
PA11Z	Acute upper respiratory tract infection and common cold	566	5	484	5	288
PA12Z	Asthma or wheezing	599	5	702	5	288
PA17A	Intermediate infections with CC	1121	5	1261	8	288
PA19A	Viral infections with length of stay 1 day or less	435	5	455	5	288
PA21A	Infectious or non-infectious gastroenteritis, with CC	1728	8	913	5	288
PA25B	Major gastrointestinal disorders without CC	1352	5	1103	5	288
PA26B	Other gastrointestinal disorders without CC	835	5	589	5	288
PA28B	Feeding difficulties and vomiting, without CC	828	5	551	5	288
PA29Z	Abdominal pain	691	5	580	5	288
PA50Z	Ingestion poisoning or allergies	453	5	503	5	288
PA58Z	Examination, follow-up, special screening or other admissions, with length of stay 0 days	427	5	346	5	288
PA63B	Head, neck and ear disorders with length of stay 1 day or more, with CC	1524	5	994	5	288
PA67Z	Diabetes, with ketoacidosis or coma	1459	10	1055	6	288
PA68Z	Diabetes, without ketoacidosis or coma	1207	5	954	5	288
PA69Z	Nephritic and nephrotic renal diseases	662	5	1350	9	288
WA21Y	Other procedures or health-care problems, without CC	467	5	579	5	198
XB07Z[b]	Paediatric critical care high dependency	1004	N/A	N/A	N/A	N/A
XB05Z[b]	Paediatric critical care intensive care basic	1670	N/A	N/A	N/A	N/A

CC, complication and comorbidity; GI, gastrointestinal; N/A, not applicable.
a Superseded in 2014/15 by FZ62A.
b Unbundled intensive-care and high-dependency HRG costs taken from the *National Schedule 2014–15*[122] and uplifted by a Hospital and Community Health Services index value of 1.7% per annum.

TABLE 19 Unit costs of patient contacts with health care[123]

Profession	Cost (£)					
	Surgery	Home	Telephone, e-mail and texts	Hospital outpatient	A&E	School visit
Advanced nurse including infusion specialist and diabetes nurse	22.75	37.92	9.10	45.50	30.33	37.92
GP	64.50	87.75	26.63	–	–	–
Social worker (children's services)	39.50	39.50	39.50	–	–	39.50
Hospital consultant	–	–	22.83	68.50	45.67	–
Specialist registrar	–	13.68	12.00	36.00	24.00	–
Community nurse	38.00	38.00	38.00	38.00	–	38.00
General practice nurse	14.75	–	5.60	–	–	–
Dietician	19.00	19.00	6.33	19.00	12.67	19.00
Psychologist	69.50	69.50	23.17	69.50	46.33	69.50

TABLE 20 Unit costs of devices and consumables

Consumable or device	Annual cost (£)	Rationale	Source
F. Hoffman-La Roche AG pump	594	Unit cost of £2375 with a 4-year lifespan	Supplier
F. Hoffman-La Roche AG pump consumables (e.g. reservoirs, cannula, batteries)	1818		Supplier
Medtronic pump	749	Unit cost of £2995 with a 4-year lifespan	Supplier
Medtronic pump consumables (e.g. reservoirs, cannula, batteries)	2377		Supplier
Pen injectors (various)	80	1 × basal and 1 × bolus at £40 each	Based on children's pen device suppliers in the UK
Needles for pen devices	87	Four injections a day at a cost of £5.95 per 100 needles	*British National Formulary*[124]
Blood glucose monitoring	577	NICE recommendation of five tests a day, Accu-Chek Aviva test strips (F. Hoffman-La Roche AG, Basel, Switzerland), at £15.79 per 50 tests	*British National Formulary*[124]

If a hospitalisation spanned a period preceding and following randomisation, an adjustment was made to apportion costs between baseline and post-baseline values. Patients who were admitted to hospital n days before randomisation and spending N days in hospital after randomisation had their total costs calculated as:

$$\text{Post-randomisation cost} = (N/n + N) \times (\text{ward cost derived from HRG}). \quad (4)$$

$$\text{Pre-randomisation cost} = (n/n + N) \times (\text{ward cost derived from HRG}). \quad (5)$$

TABLE 21 Unit costs of insulins taken from the *British National Formulary*[124]

Insulin	Type	Cost (£ per unit)
Insulin aspart (Novorapid®, Novo Nordisk Ltd, Gatwick, UK)	Short acting	0.0141
Insulin detemir (Levemir®, Novo Nordisk Ltd, Gatwick, UK)	Intermediate/long acting	0.0290
Insulin aspart/protamine-crystallised insulin aspart in the ratio 30 : 70 (NovoMix 30, Novo Nordisk Ltd, Gatwick, UK)	Short/intermediate acting	0.0199
Insulin lispro (Humalog®, Eli Lilly and Company Ltd, Basingstoke, UK)	Short acting	0.0166
Insulin glargine (Lantus®, Sanofi, Guildford, UK)	Intermediate/long acting	0.0307
Biphasic isophane insulin (Humulin® M3, Eli Lilly and Company Ltd, Basingstoke, UK)	Short/intermediate acting	0.0166

Training comprised multiple sessions covering single visits. Although full details of how many patients and their family members attended each training session were not recorded, the majority were believed to be one-to-one sessions. However, because the majority of training was conducted in outpatient clinics, the costs of training were excluded from the total to avoid the potential for double-counting.

Blood glucose monitoring was costed on the minimum NICE recommendation of five tests per day.[19] Identical blood glucose monitoring costs were added to the consumables costs supplied by the pump manufacturers for the CSII intervention group. The costs of consumables in the MDI intervention group comprised blood glucose monitoring and disposable needles, based on an estimate of four insulin injections a day.[19] Total costs for each patient were calculated from the sum of the costs of ward, outpatient care, A&E, primary care, device, consumables and prescribed insulin.

Patients' use of health-care resources and total costs were calculated for the ITT population, with summary statistics generated by intervention group.

Outcomes

Within-trial QALYs were calculated as the area under the utility–time curve over 12 months, with utilities calculated from patients' (aged ≥ 12 years) or their parents' or guardians' responses to the HUI questionnaire taken at baseline and then at 3-, 6-, 9- and 12-month visits. The HUI questionnaire has been validated in paediatric populations[126,127] and was previously suggested by NICE for use in children,[128] and considers the six attributes of sensation, mobility, emotion, cognition, self-care and pain. These further expand into vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain using the Sheffield algorithm, which was used to generate a single UK-derived preference-based utility score.[129]

The parents of patients < 3 years of age at randomisation were not required to answer the HUI questionnaire. Proxy assessment is recommended for the 3- to 12-year-old category, and self-assessment and/or proxy is recommended for patients > 12 years of age.

The minimum requirements for the base-case calculation of QALYs were utility measurements at baseline and at 12 months, with linear interpolation for any missing data points in between. When both parents and patients completed a HUI questionnaire in the same visit, base-case preference was given to the patient if they were aged 12 years and over at randomisation, and to the parent or guardian if the patient was under 12 years old.

Incremental analysis

In the base-case analysis, the cost-effectiveness of CSII was evaluated by its ICER calculated according to the formula:

$$\text{ICER} = \Delta\text{Costs}/\Delta\text{QALY}, \tag{7}$$

in which, ΔCosts is the difference in mean total costs between intervention groups and ΔQALY is the difference in mean QALYs between intervention groups.

Uncertainty analysis

Mean costs and QALYs and differences between intervention groups in costs and QALYs were based on a bootstrapped analysis (bias-corrected and accelerated) using 10,000 replicates. The 95% central range was based on the 2.5 and 97.5 percentiles of the bootstrap values.

Uncertainty in the ICER was represented in cost-effectiveness acceptability curves, which presented the probability of CSII being cost-effective for given ceiling thresholds of costs per QALY.[130]. Estimates of ICERs were compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness set by NICE.[131]

Sensitivity analysis

Robustness of the base-case analysis was tested with respect to costs by (1) applying 2- and 6-year life cycles to the pumps, whereby the purchase cost of the pump was divided by 2 and 6 and (2) considering insulin costs based on quantity administered.

Sensitivity analyses concerning outcomes used (1) utilities and QALYs based on HUI3-derived Canadian tariff scores[132] and (2) mean baseline utility imputation and multiple imputation with chained equations (MICE)[133] to assess the impact of missing data on HUI2-derived scores. Explanatory variables considered included (1) utility at baseline and at 3 and 6 months; (2) QALYs calculated up to 9 months, centre, baseline cost, age, ethnicity, sex, weight, blood pH, blood glucose and HbA_{1c} concentration; (3) mean baseline utility imputation and the last observation carried forward (LOCF) approach, as recommended in the HUI manual;[132] and (4) HUI2-derived full parental or full patient responses to the HUI questionnaires.

All analyses adhered to the health economics analysis plan (see *Appendix 3*), and were performed using Stata® version 13 (StataCorp LP, College Station, TX, USA), and reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[134]

Exploratory analysis

The contribution of the baseline variables, of age group, centre, BMI, sex, baseline cost and ethnicity to total costs and of age group, centre, BMI, sex, baseline utility and ethnicity to QALYs, were tested separately in regression models. This allowed for identification of any particular high-cost subgroup and adjustment for any imbalanced covariates to account for their confounding effect.[135] Given the expected non-normality of both costs and QALYs, generalised linear models were implemented using a range of families and links and goodness of fit established using the Modified Park test.

A further planned exploratory analysis was to extrapolate the trial results to estimate lifetime costs and benefits and to capture long-term microvascular and macrovascular complications using the CDM model.[136] This extrapolation was to use a 3.5% annual discount rate for costs and outcomes accruing after the first year.[131] Clinical and physiological progression parameters were to be as presented in the NICE guideline[19] and updated with relevant data from the SCIPI study.

Results

Resource use and costs

Complete resource use data were available for all patients.

Patients' use of health-care resources and corresponding NHS costs were comparable in both intervention groups for the 3 months preceding randomisation (*Table 22*). The mean cost in the CSII group was £1530 (95% CI £1408 to £1779), compared with £1392 (95% CI £1267 to £1530) in the MDI intervention group. Although there were more hospital outpatient visits in the CSII group, there was no difference in

TABLE 22 Resource use in the 3 months prior to randomisation

Item of resource use (units)	Treatment arm, mean (95% CI)		
	CSII ($n = 144$)	MDI ($n = 149$)	Difference (95% CI)
Health-care professional contacts (number of telephone calls, faxes, texts or e-mails)	3.32 (2.7 to 3.97)	2.58 (1.96 to 3.3)	0.74 (–0.18 to 1.65)
Scheduled outpatient (number of visits)	1 (1 to 1)	1 (1 to 1)	0 (0 to 0)
Unscheduled outpatient visits (number of visits)	2.19 (1.77 to 2.63)	1.12 (0.89 to 1.37)	1.07 (0.6 to 1.59)
A&E department (number of attendances)	0.77 (0.56 to 0.99)	0.62 (0.42 to 0.88)	0.15 (–0.18 to 0.46)
Other hospital (e.g. ward visits) (number)	0.49 (0.2 to 0.82)	0.44 (0.18 to 0.79)	0.04 (–0.38 to 0.47)
GP visits (number of contacts)	0.25 (0.17 to 0.34)	0.21 (0.14 to 0.28)	0.04 (–0.07 to 0.16)
Home visits (number of contacts)	1 (0.78 to 1.24)	0.99 (0.75 to 1.25)	0.01 (–0.33 to 0.34)
School visits (number of contacts)	0.3 (0.2 to 0.41)	0.24 (0.17 to 0.32)	0.06 (–0.07 to 0.19)
Training sessions (recorded sessions)	14.6 (12.99 to 16.22)	13.83 (12.7 to 14.99)	0.77 (–1.17 to 2.74)
HRG code			
PA21A Infectious or non-infectious gastroenteritis, with CC	0.02 (0 to 0.05)	0 (0 to 0)	0.02 (0 to 0.04)
PA67Z Diabetes, with ketoacidosis or coma	0.13 (0.07 to 0.2)	0.11 (0.06 to 0.17)	0.02 (–0.07 to 0.11)
PA68Z Diabetes, without ketoacidosis or coma	0.74 (0.65 to 0.83)	0.72 (0.64 to 0.81)	0.02 (–0.1 to 0.14)
PA69Z Nephritic and nephrotic renal diseases	0 (0 to 0)	0.01 (0 to 0.02)	–0.01 (–0.02 to 0)
XB05Z Paediatric critical care intensive care basic	0.01 (0 to 0.02)	0.02 (0 to 0.06)	–0.01 (–0.06 to 0.03)
XB07Z Paediatric critical care high dependency	0.15 (0.03 to 0.32)	0.05 (0.01 to 0.11)	0.09 (–0.04 to 0.27)

CC, complication and comorbidity.

the mean total costs of these visits (£189, 95% CI –£29 to £417). The main cost drivers for the 3 months preceding randomisation were inpatient stays (contributing to 69% of the total) and training sessions (contributing to 14%), which were carried out primarily as outpatient appointments.

Resource use for the 12 months following randomisation is reported in *Table 23*. Inpatient stays and A&E department visits decreased considerably relative to the 3 months preceding randomisations, although health-care professional contacts, especially outpatient and GP clinic visits, and contacts via texts, e-mails and telephone calls increased.

Patients who were randomised to CSII had more than twice as many A&E department visits and inpatient stays relating to the management of diabetes (HRG code PA68Z) as those in the MDI group, although the absolute numbers of attendances were low (*Table 24*). Over the 12-month period, health-care professionals made an average of 4.3 (95% CI 0.6 to 8.0) more contacts by text, e-mail or telephone with patients in the CSII group than with patients in the MDI group.

Data on prescribed insulin were available for all but seven patients; for these patients, data on dose administered were used in the analysis. There were no significant differences in either the quantity or the cost of prescribed insulin between the two intervention groups.

TABLE 23 Resource use in the 12 months after randomisation

Item of resource use (units)	Treatment arm, mean (95% CI)		
	CSII ($n = 144$)	MDI ($n = 149$)	Difference (95% CI)
Health-care professional contacts (number of telephone calls, faxes, texts or e-mails)	21.15 (18.31 to 23.99)	16.87 (14.62 to 19.25)	4.29 (0.64 to 7.98)
Scheduled outpatient (number of visits)	4 (4 to 4)	4 (4 to 4)	0 (0 to 0)
Unscheduled outpatient visits (number of visits)	10.85 (9.6 to 12.08)	10.81 (9.65 to 11.98)	0.05 (–1.63 to 1.73)
A&E department (number of attendances)	0.85 (0.51 to 1.24)	0.4 (0.24 to 0.58)	0.44 (0.07 to 0.88)
Other hospital (e.g. ward visits) (number)	0.33 (0.1 to 0.67)	0.26 (0.11 to 0.44)	0.06 (–0.23 to 0.43)
GP visits (number of contacts)	1.46 (1.16 to 1.78)	1.2 (0.99 to 1.42)	0.26 (–0.11 to 0.64)
Home visits (number of contacts)	2.45 (1.91 to 3.1)	1.99 (1.6 to 2.42)	0.46 (–0.23 to 1.22)
School visits (number of contacts)	1.4 (1.14 to 1.69)	1.5 (1.19 to 1.85)	–0.1 (–0.53 to 0.32)
Training sessions (recorded sessions)[a]	24.79 (21.87 to 27.92)	22.45 (19.38 to 25.54)	2.34 (–1.89 to 6.61)
Insulin (mean prescribed daily units)	71.61 (62.76 to 81.78)	66.32 (58.81 to 74.2)	5.05 (–6.6 to 17.53)
HRG code			
FZ62Z Diagnostic and intermediate procedures on the upper GI tract	0.01 (0 to 0.02)	0.02 (0 to 0.05)	–0.01 (–0.04 to 0.02)
PA21A Infectious or non-infectious gastroenteritis, with CC	0.01 (0 to 0.03)	0.01 (0 to 0.02)	0.01 (–0.01 to .[b])
PA25B Major gastrointestinal disorders without CC	0.02 (0 to 0.05)	0.01 (0 to 0.02)	0.01 (–0.01 to 0.05)
PA67Z Diabetes, with ketoacidosis or coma	0 (0 to 0)	0.01 (0 to 0.02)	–0.01 (–0.02 to .[b])
PA68Z Diabetes, without ketoacidosis or coma	0.17 (0.08 to 0.27)	0.07 (0.03 to 0.12)	0.09 (0 to 0.21)
Other HRGs	0.09 (0.04 to 0.15)	0.07 (0.03 to 0.12)	0.02 (–0.06 to 0.09)

CC, complication and comorbidity; GI, gastrointestinal.
a Training sessions were not included in the total cost, as they were recorded as contacts with health-care professionals.
b Not computable owing to small sizes.

Mean total and disaggregated costs, with their 95% bootstrapped CIs, are reported in *Table 25*. Consumables, devices (for insulin pumps) and inpatient stays were the main drivers of the differences in costs between the groups. These contributed 63%, 28% and 9%, respectively. Each of these was higher in the CSII group. The annualised cost of the devices differed by £520 between groups; consumables, which included needles, infusion sets and reservoirs, differed by £1177 (£1841 CSII vs. £664 MDI).

The mean total 12-month costs for CSII were £4404 (median £4010, range £2995–13,175, 95% CI £4197 to £4642, $n = 144$) and for MDI were £2541 (median £2351, range £1295–5930, 95% CI £2412 to £2672, $n = 149$).

Disaggregated costs for prescribed insulin, outpatient visits and GP visits were not significantly different between the intervention groups and the extra costs associated with A&E department visits and electronic communications made only a modest (2.3%) contribution to the overall difference in mean total costs (£1863, 95% CI £1620 to £2137). The costs of training, covering the period from 15 days prior to randomisation to the end of follow-up, were £1230 (95% CI £1125 to £1337) in the CSII group and £1001 (95% CI £905 to £1100) in the MDI group.

TABLE 24 Disaggregated and total costs in the 12 months after randomisation

Item of resource use	Treatment arm, mean cost (£) (95% CI)		Difference in mean cost (£) (95% CI)
	CSII ($n = 144$)	MDI ($n = 149$)	
Consumables (e.g. needles, infusion sets, reservoirs)	1841 (1826 to 1861)	664 (664 to 664)	1177 (1162 to 1197)
Device (pump 4-year lifespan or two pen devices)	600 (596 to 606)	80 (80 to 80)	520 (516 to 526)
Insulin (prescribed)	422 (364 to 486)	482 (426 to 541)	–60 (–142 to 24)
Health-care professional contacts (telephone calls, faxes, texts or e-mails)	138 (117 to 162)	108 (92 to 124)	30 (3 to 59)
Scheduled outpatients visits	434 (434 to 434)	434 (434 to 434)	0 (0 to 0)
Unscheduled outpatient visits	309 (272 to 346)	328 (292 to 366)	–19 (–71 to 33)
Inpatient stays costed from HRG codes	387 (245 to 553)	219 (142 to 306)	168 (5 to 352)
A&E	26 (16 to 39)	13 (8 to 19)	13 (2 to 27)
Other hospital (e.g. ward visits)	3 (1 to 7)	3 (1 to 5)	1 (–3 to 5)
GP visits	71 (56 to 88)	57 (45 to 69)	15 (–5 to 35)
Home visits	106 (80 to 138)	83 (66 to 100)	23 (–9 to 59)
School visits	53 (43 to 64)	56 (44 to 69)	–3 (–19 to 13)
Concomitant medications	12 (8 to 17)	15 (8 to 23)	–2 (–12 to 6)
Total cost	4404 (4197 to 4642)	2541 (2412 to 2672)	1863 (1620 to 2137)

TABLE 25 Incremental analysis of the cost-effectiveness of CSII

	Treatment arm, mean (95% CI)			
	CSII ($n = 109$)	MDI ($n = 105$)	Difference, mean (95% CI)	ICER
Costs (£)	4404 (4197 to 4642)	2541 (2412 to 2672)	1863 (1620 to 2137)	CSII dominated
QALYs	0.910 (0.892 to 0.927)	0.916 (0.899 to 0.933)	–0.006 (–0.031 to 0.018)	

Health utilities and quality-adjusted life-years

The HUI questionnaires were not completed for all patients. Thirteen of the 14 patients for whom there were no HUI data were aged < 3 years at randomisation and so were excluded from the analysis. Baseline utilities were missing for 23 patients in the CSII group and 14 patients in the MDI group.

For patients with complete baseline utility assessment, mean values were 0.870 (95% CI 0.847 to 0.892, $n = 115$) for the CSII group, compared with 0.888 (95% CI 0.866 to 0.909, $n = 127$) for the MDI group. Two hundred and fourteen patients (CSII group, $n = 109$; MDI group, $n = 105$) were included in the base-case analysis. Changes in utilities and each of the HUI domains (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain) over the 12-month period are presented in *Figures 7* and *8*, respectively. Both intervention groups provided improvements in patients' happiness (emotion) and how they perceived pain perception. However, there were no significant differences in QALYs between intervention groups. For the CSII group, these were 0.910 QALYs (95% CI 0.892 to 0.927 QALYs), and for the MDI group these were 0.916 QALYs (95% CI 0.899 to 0.933 QALYs), which was a difference of –0.006 QALYs (95% CI –0.031 to 0.018 QALYs).

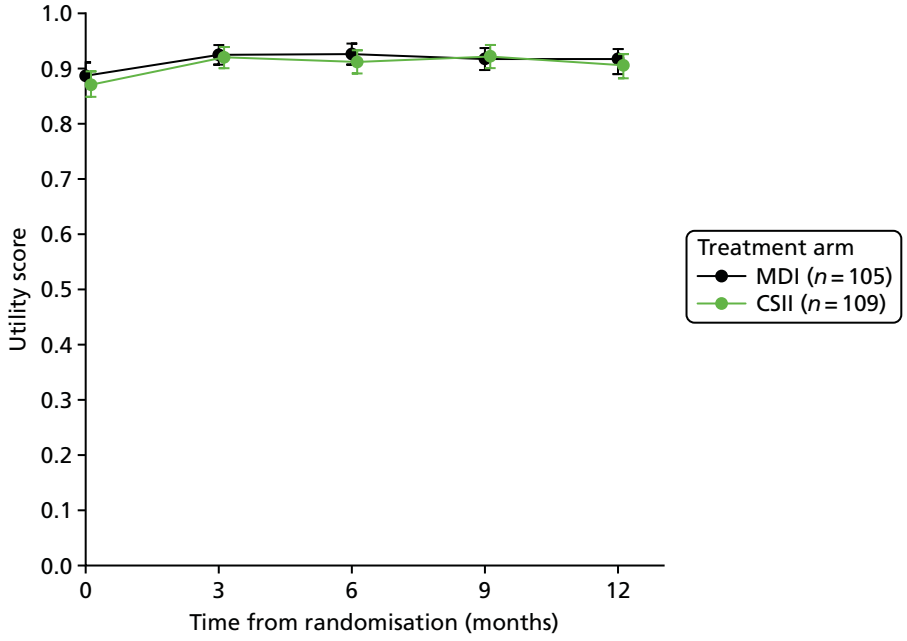

FIGURE 7 Mean utility values (95% CI) over 12 months for the base-case analysis.

Incremental analysis

The ICER is indeterminate, as CSII was dominated by MDI over the 12-month time horizon of analysis (see *Table 25*). As the differences in costs favoured MDI (£1863 less expensive) and as there was no difference in benefits (–0.006 QALYs), through cost minimisation, MDI is more cost-effective.

Uncertainty analysis

The cost-effectiveness plane, which presents the difference in costs on the vertical axis and difference in effects on the horizontal axis, is shown in *Figure 9*. Sixty-nine per cent of iterations were in the north-west quadrant, reflecting the probability of CSII being dominated by MDI. The corresponding cost-effectiveness acceptability curve (*Figure 10*) indicates that CSII is not cost-effective, even at very high thresholds, consistent with the certainty of there being a large cost difference with no improvement in QALYs.

Sensitivity analysis

An assumption of insulin pumps being replaced every 2 years increased the cost difference between CSII and MDI to £2463 (95% CI £2218 to £2738), but although less frequent replacement (every 6 years) lowered the cost difference to £1663 (95% CI £1420 to £1937), CSII remained dominated.

An analysis based on the quantity of insulin administered, as opposed to prescribed, resulted in a mean cost of £4102 (95% CI £3915 to £4318) in the CSII group and £2192 (95% CI £2080 to £2310) in the MDI group, which was a difference of £1910 (95% CI £1690 to £2151).

All sensitivity analyses concerning the calculation of QALYs consistently indicated that there was no difference over 12 months (*Table 26*). Based on the Canadian tariff HUI3 scores, the difference between group means (CSII – MDI) was –0.004 QALYs (95% CI –0.036 to 0.029 QALYs). Alternative approaches for dealing with missing data, in which 29 additional patients in the CSII group and 36 additional patients in the MDI group were included, yielded similar QALY differences. Using MICE, this was –0.004 QALYs (95% CI –0.022 to 0.014 QALYs) and, based on LOCF, the difference was –0.001 QALYs (95% CI –0.022 to 0.020 QALYs). HUI2-derived QALY differences based on full parental and full patient responses to the HUI questionnaires were, respectively, –0.001 QALYs (95% CI –0.024 to 0.023 QALYs) and –0.006 QALYs (95% CI –0.031 to 0.018 QALYs).

None of the sensitivity analyses affected the base-case result of CSII being dominated by MDI.

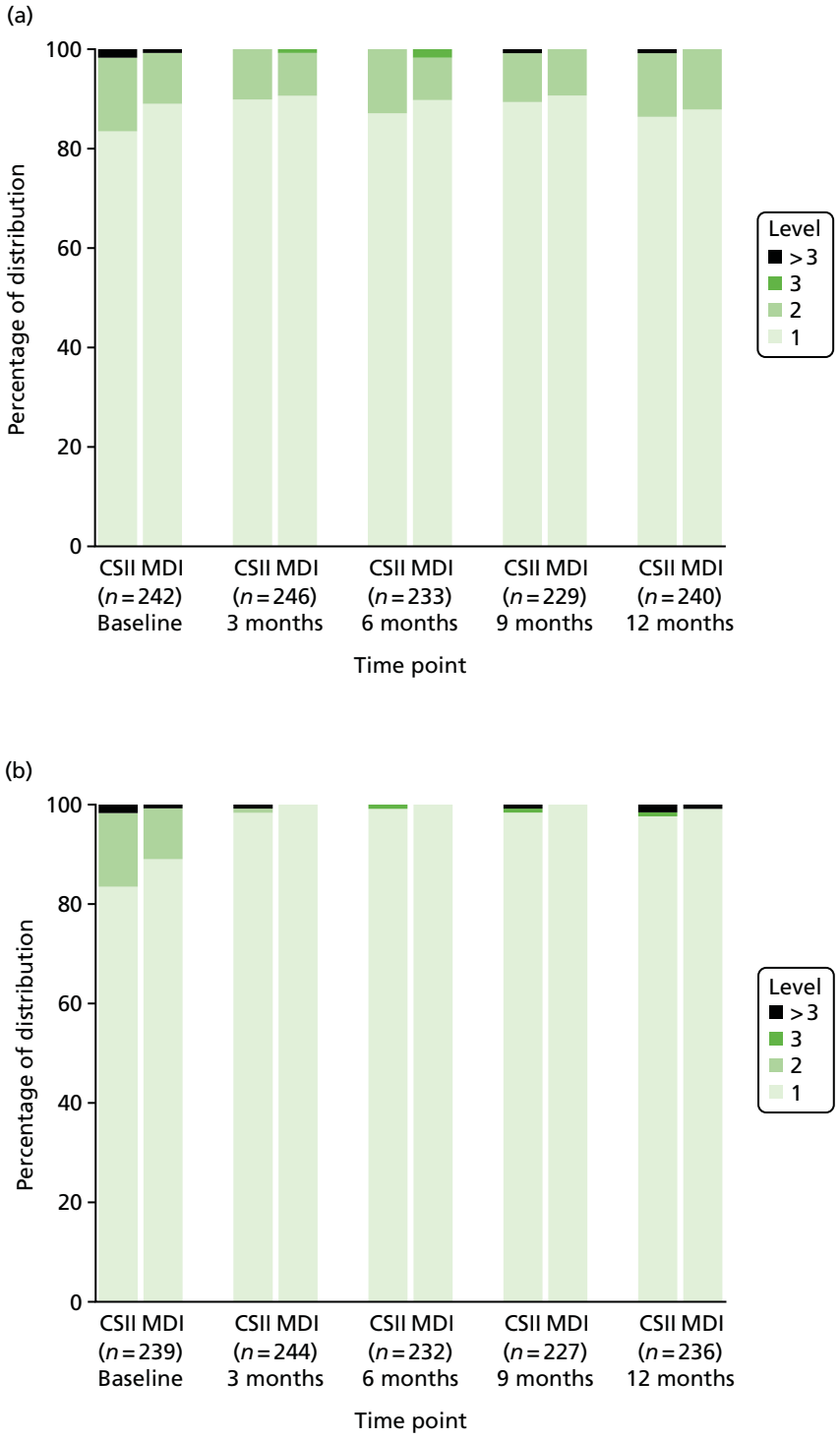

FIGURE 8 Distribution of responses to HUI domain, by intervention group, over time. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotion; (g) cognition; and (h) pain. (*continued*)

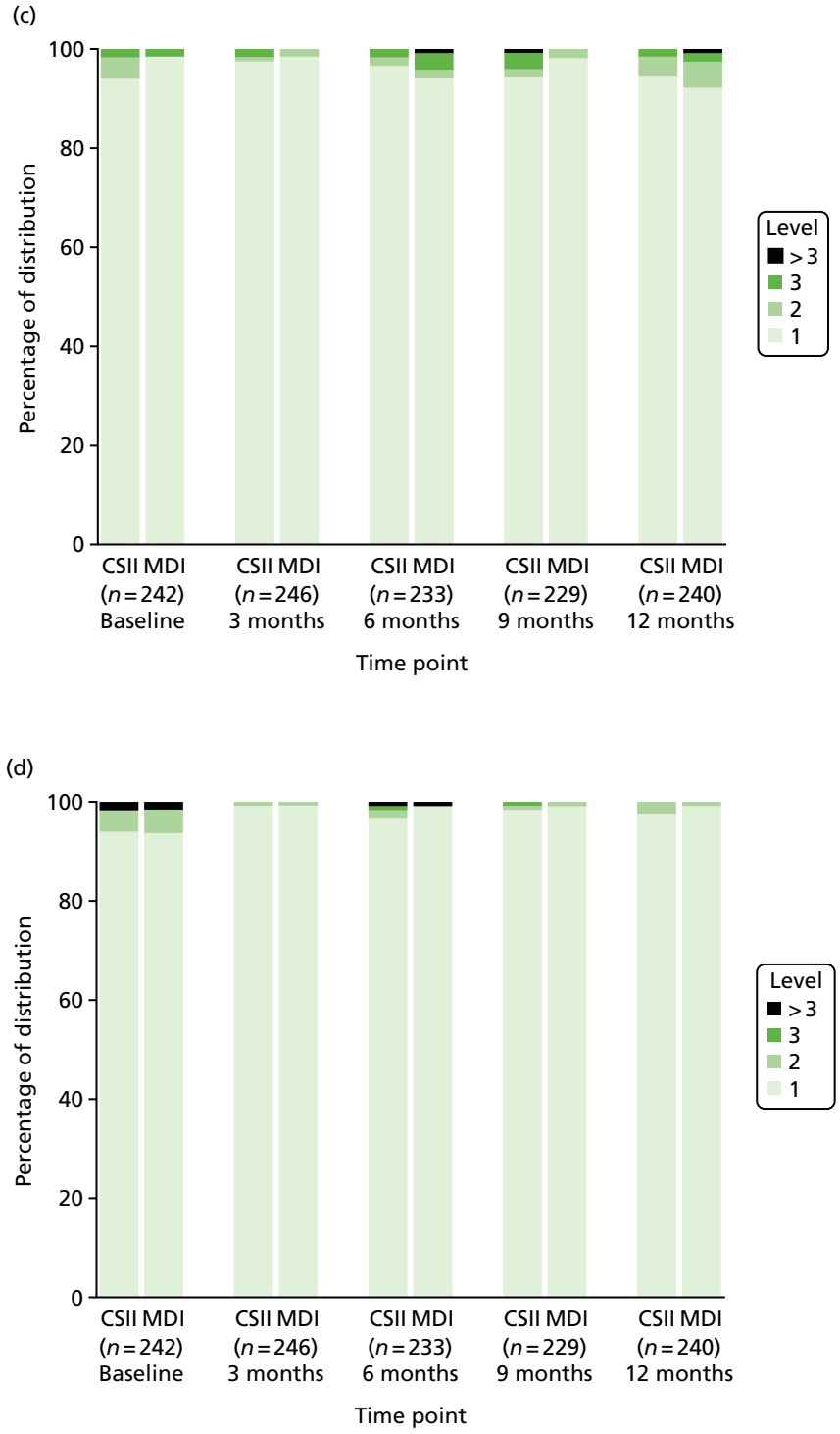

FIGURE 8 Distribution of responses to HUI domain, by intervention group, over time. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotion; (g) cognition; and (h) pain. (*continued*)

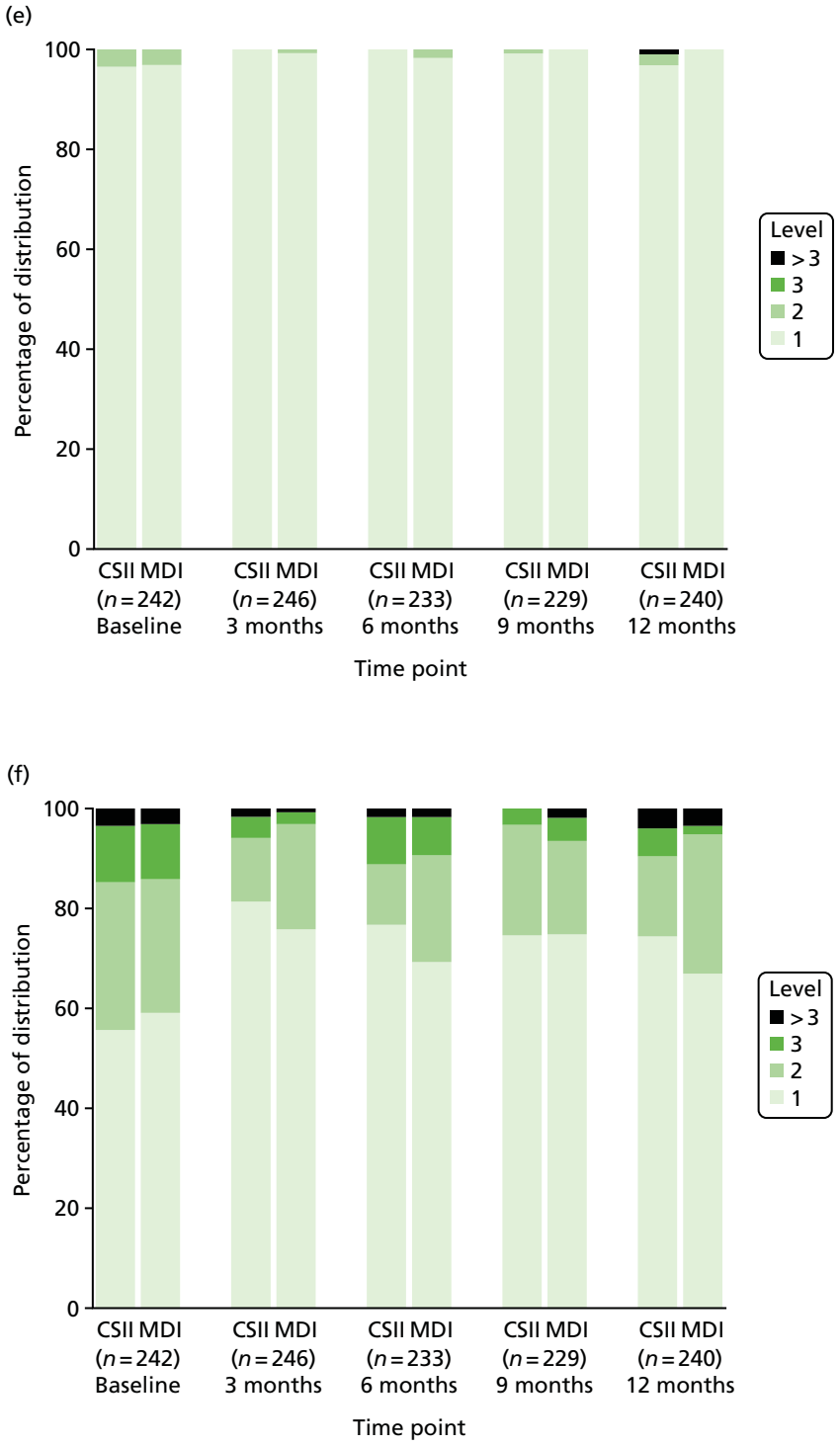

FIGURE 8 Distribution of responses to HUI domain, by intervention group, over time. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotion; (g) cognition; and (h) pain. (*continued*)

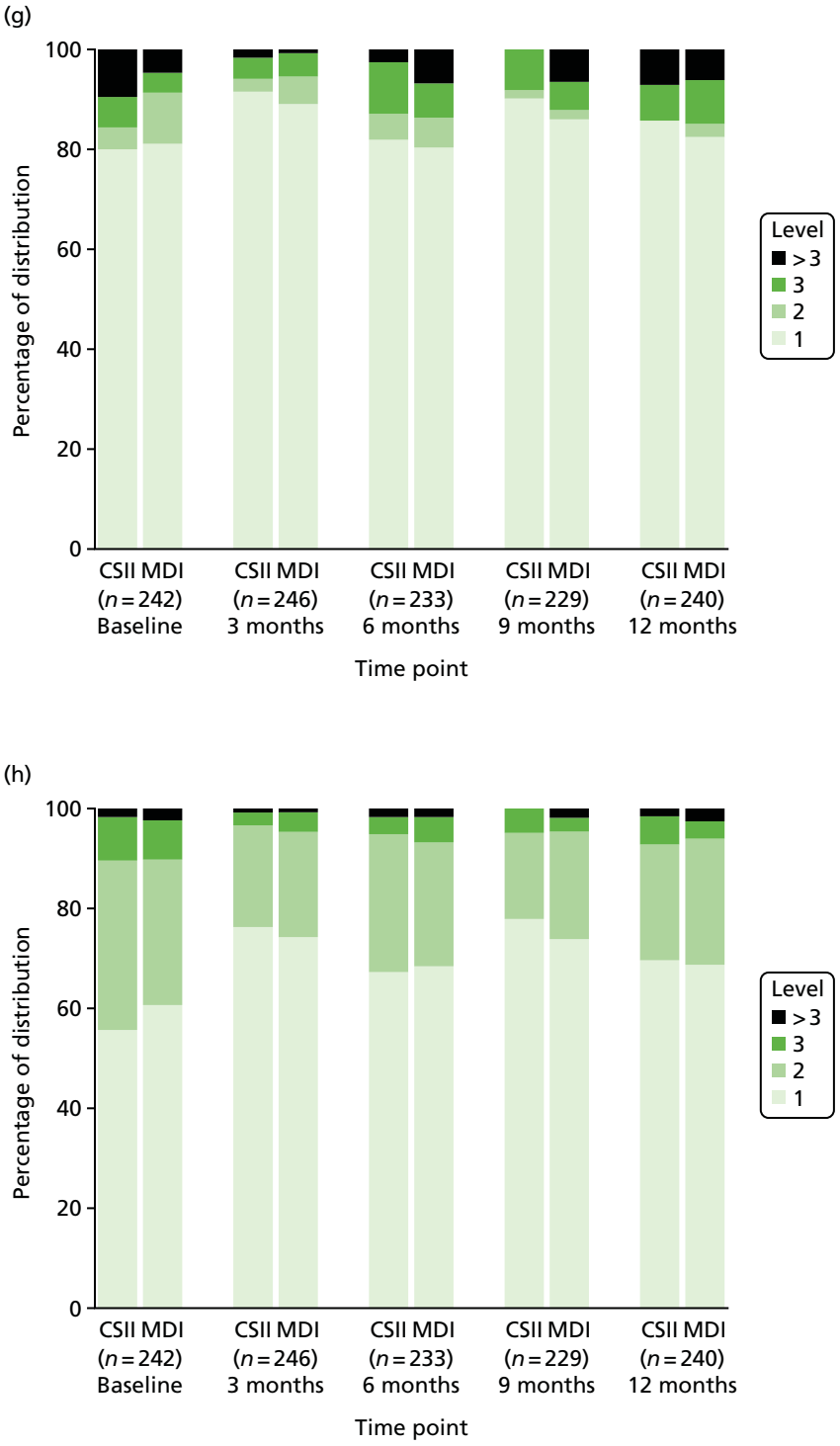

FIGURE 8 Distribution of responses to HUI domain, by intervention group, over time. (a) Vision; (b) hearing; (c) speech; (d) ambulation; (e) dexterity; (f) emotion; (g) cognition; and (h) pain.

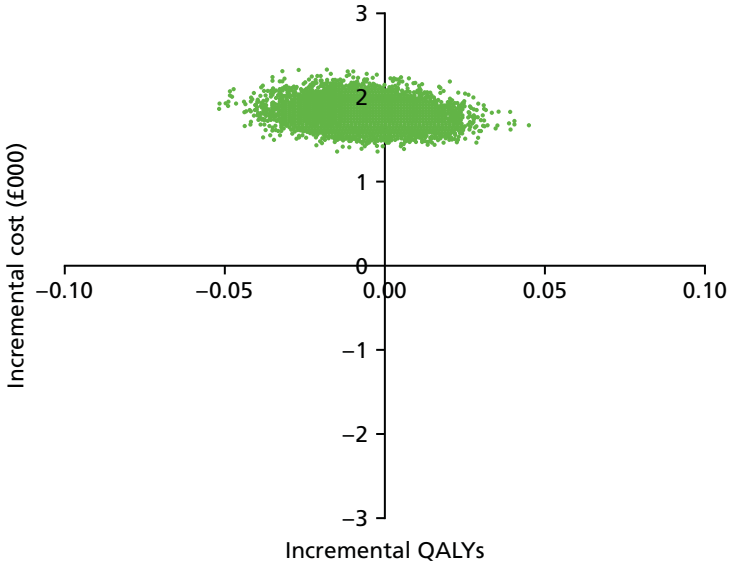

FIGURE 9 Cost-effectiveness plane presenting the joint uncertainty in incremental costs and QALYs.

Exploratory analysis

Cost distributions for both intervention groups deviated from normality, with *p*-values for both skewness and kurtosis normality testing being < 0.01. However, based on the Akaike information criterion for different model specifications, an ordinary least squares regression was optimal for both costs and QALYs.

In the cost regression, 46% of the variability in total costs could be explained, with intervention group, recruiting centre and pre-randomisation costs being significant. The adjusted cost difference between the intervention groups was comparable to the base-case analysis at £1850 (95% CI £1600 to £2100).

In the QALY regression, 41% of the variability in total costs could be explained, with only baseline utility being significant. The adjusted difference in QALYs between intervention groups was consistent with the base-case analysis at 0.000 QALYs (95% CI –0.019 to 0.020 QALYs).

As there were no differences between intervention groups in HbA_{1c} concentrations at 12 months, and no indication of CSII being cost-effective given the large difference in cost, longer-term extrapolation was considered to be futile, especially given the lack of validation of diabetes models in children.

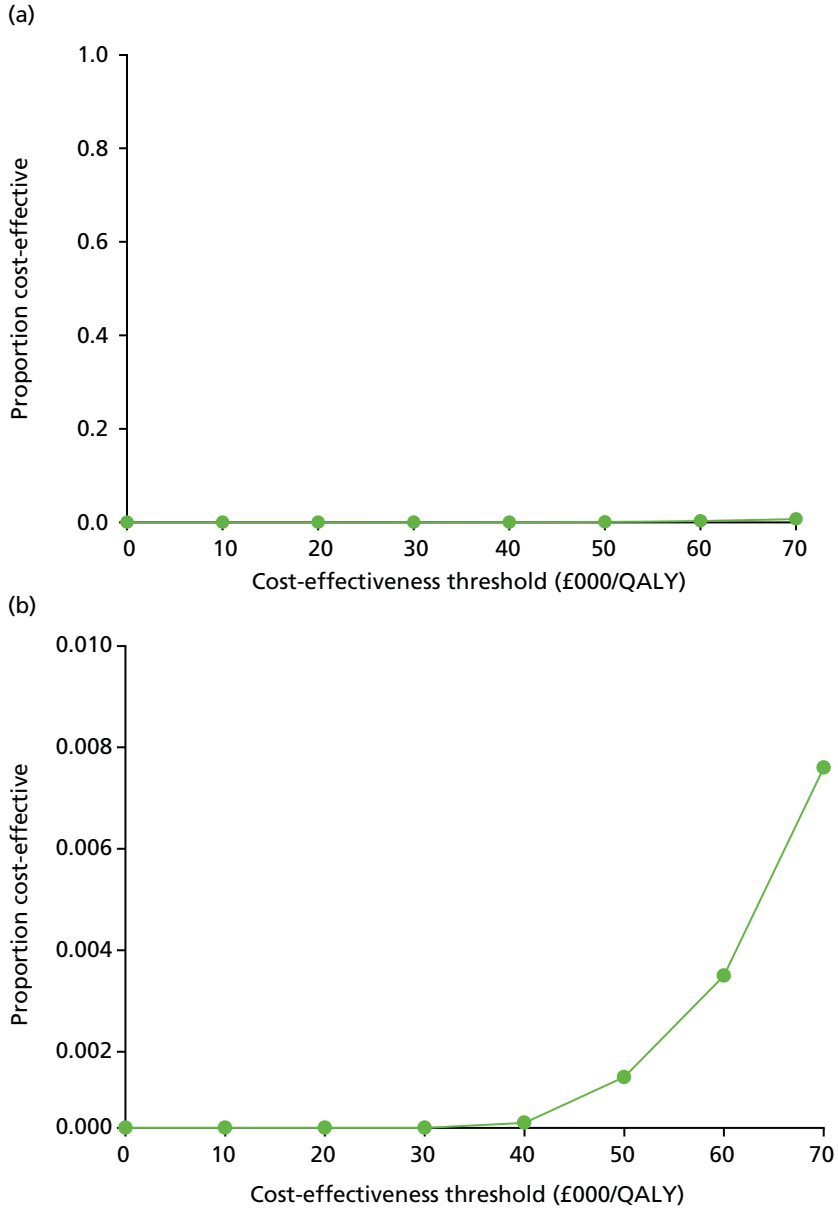

FIGURE 10 Cost-effectiveness acceptability curve indicating the probability of CSII being cost-effective for different thresholds of cost-effectiveness. (a) Proportion 0–1; and (b) proportion 0–0.01.

TABLE 26 Sensitivity analyses for different methods of calculating QALYs and consideration of missing data

	Treatment arm				
	CSII		MDI		
Scenario	*n*	Mean (95% CI)	*n*	Mean (95% CI)	Difference, mean (95% CI)
QALYs (base case)	105	0.910 (0.892 to 0.927)	109	0.916 (0.899 to 0.933)	–0.006 (–0.031 to 0.018)
QALYs (Canadian tariffs)[a]	105	0.908 (0.884 to 0.929)	109	0.912 (0.887 to 0.933)	–0.004 (–0.036 to 0.029)
MICE-imputed QALYs	138	0.910 (0.896 to 0.923)	141	0.915 (0.903 to 0.926)	–0.004 (–0.022 to 0.014)
LOCF-imputed QALYs	138	0.911 (0.896 to 0.925)	141	0.912 (0.896 to 0.926)	–0.001 (–0.022 to 0.020)
Parental QALYs	105	0.914 (0.897 to 0.930)	109	0.915 (0.899 to 0.931)	–0.001 (–0.024 to 0.023)
Child QALYs	105	0.910 (0.892 to 0.927)	109	0.916 (0.899 to 0.932)	–0.006 (–0.031 to 0.018)

a Derived using HUI3 algorithm, all other scores derived using HUI2 algorithm.

Chapter 5 Discussion

Summary of findings

The results of the SCIPI study clearly demonstrate that, across the range of ages from 7 months to 15 years, treatment with CSII is not superior to treatment with MDI during the first year of treatment for T1D and is not a cost-effective treatment. At 12 months following diagnosis, HbA_{1c} concentrations differed by only 2.4 mmol/mol ($p = 0.1$), being lower in participants treated with MDI and with our study having been powered to detect a difference of > 0.5%, approximately 5 mmol/mol. The percentage of participants whose HbA_{1c} concentration was within the target range (< 48 mmol/mol) at 12 months differed between the treatment arms by 5% (CSII, 15.4%; MDI, 20.4%) and was also not significantly different ($p = 0.28$).

The proportion of patients in the CSII group who experienced AEs (28%) was nearly three times that in the MDI group (10%). During the course of the study, there were 11 severe AEs (nine episodes of severe hypoglycaemia and two of DKA), of which nine occurred in patients treated with CSII.

Patient-reported disease-related QoL did not differ between treatment arms, although parent-reported measures of QoL showed higher scores for patients who were treated with CSII, indicating a superior QoL. However, it should be noted that child-reported QoL starts from age 5 years, whereas the parent-reported QoL starts from age 2 years, and that, in general, the size of the differences and CI widths are similar between child- and parent-reported measures.

Patients randomised to CSII had more than twice as many A&E department visits and inpatient stays relating to the management of T1D as those in the MDI group. Over the 12-month period, health-care professionals had, on average, 4.3 (95% CI 0.6 to 8.0) more contacts (texts, e-mails and telephone calls) with participants in the CSII group than with those in the MDI group. The mean total costs were £1863 (95% CI £1620 to £2137) higher in the CSII group than in the MDI group, with the majority of this difference (£1177) attributable to the additional cost of consumables and device (annualised cost of £600 for CSII vs. £80 for pen devices). There were no significant differences in QALYs between the CSII and MDI groups (–0.006 QALYs, 95% CI –0.031 to 0.018 QALYs).

In summary, the SCIPI study achieved excellent completeness of primary outcome data for assessment of efficacy of CSII compared with MDI. There were no differences in key baseline characteristics between groups at randomisation. There was no difference in efficacy between CSII and MDI in any of the primary ITT analyses. In addition, there was no difference in efficacy between CSII and MDI in the per-protocol ITT analyses. The economic evaluation indicated that CSII does not represent a cost-effective option for the management of T1D in patients representative of the SCIPI study population. There was also no evidence of a difference in QALY gain over the 12-month period of observation in participants treated with CSII compared with those receiving MDI, and the cost differential was such that, even for willingness-to-pay values far in excess of the NICE £30,000 per QALY threshold for cost-effectiveness, CSII remained dominated by MDI.

Patient recruitment and retention

The large and diverse population of patients recruited to the SCIPI study, coupled with a high retention rate (97%), enabled us to overcome elements of bias inherent in previous RCTs and observational studies. The characteristics of study participants show that the treatment arms were well balanced for factors known to influence glycaemic control, including deprivation score, sex and ethnicity. Screening log data show that these characteristics were also well balanced between the groups of patients who consented to

participate in the study and those who declined. The distribution of ages in the study population reflects the known demographic of childhood T1D, with approximately 50% of participants being in the age range of 5–12 years.

Of those who declined to participate, most (66%) cited a strong preference to continue treatment with MDI, although a smaller number (9%) cited a strong preference for CSII. We noted that the small number of patients and parents who declined to participate in the study, stating a strong preference for CSII ($n = 36$), had a higher deprivation index (were more deprived) than those who declined stating a strong preference for MDI ($n = 259$) and those who participated in the study. National database studies[37–39] report an association with CSII use and deprivation, with the most deprived patients being least likely to be treated with CSII. Our data suggest that this association is established sometime later after the diagnosis of T1D.

Recruitment rates showed marked variability between study sites, ranging from 16% to 82% of eligible patients. Both the highest- and lowest-recruiting centres had participated in the DECIDE trial[68] and so were experienced in the recruitment of paediatric patients to research studies at the time of diagnosis of T1D. In the lowest-recruiting centre, intensive insulin therapy was introduced later in the first year of treatment and patients were treated with four or fewer injections per day at the time of diagnosis. A requirement to either increase the number of injections or to learn a new method of insulin delivery is likely to have been least attractive to this population.

We recognised that patients who were given information about the study closest to the time of diagnosis were more likely to consent than those who were approached later. This may be because a preference for MDI had yet to be established or may reflect qualities of the research staff that increased the likelihood of patients consenting to participate in the study.

We speculate that the strong preference that patients stated for MDI at the time they were invited to participate in the study is likely to be temporary. It would have been ideal to undertake qualitative work to understand more about the reasons for this preference and how it may change over time. A higher recruitment rate may have been achieved had the window for recruitment been increased to 1 month from diagnosis.

These observations underscore the difficulty in predicting recruitment rates to clinical trials. The target recruitment rate of 50% was set, in part, to ensure that a highly selected cohort of patients was not recruited. Despite our lower recruitment rate, we have been able to demonstrate that the characteristics of those who consented to participate did not differ significantly from those who declined, and we are confident that we have studied a population of patients representative of the background population of paediatric patients treated for T1D in the NHS setting.

The non-participation of patients with a strong preference for one treatment arm may limit the generalisability of our data. It would be interesting to learn more about the reasons behind this strong preference early in the diagnosis of T1D and how this may change over time. A qualitative component within the SCIPI study would have been beneficial.

By randomly allocating treatment to either MDI or CSII, we have overcome the bias in observational studies, in which treatment selection by patients, carers and health-care professionals results in over-representation of favourable patient characteristics in those treated with CSII and under-representation of these characteristics in those treated with MDI.

Previous RCTs of CSII and MDI have recruited patients with established T1D already being treated with MDI, and have randomised them to continue with MDI treatment or to change to CSII treatment. This recruitment strategy may introduce bias in favour of CSII, as patients who are satisfied with treatment with MDI and who have good glycaemic control are less likely to be approached or to participate in the study than those in whom treatment is less satisfactory. Furthermore, previous experience of treatment success or failure with

MDI may influence treatment outcomes: if a patient dissatisfied with MDI treatment consents to participate in a RCT, it is possible that randomisation to CSII will result in renewed commitment to the management of T1D; however, randomisation to continue unsatisfactory treatment with MDI may result in further disengagement. Another factor to consider is the extent to which any studies reporting benefits of CSII over MDI in established patients reflect the effects of the intensive education and increased contact with health-care professionals required before starting CSII rather than inherent benefits arising directly from CSII. These possible effects on outcomes were balanced in our study design by the selection of newly diagnosed patients, all of whom would have required a similar intensity of education. We elected to recruit patients at diagnosis of T1D to overcome this element of bias. However, it may be that the generalisability of our findings beyond the first year of T1D is therefore limited.

Fifty-three patients moved between treatment arms: 30 changed from MDI to CSII, 22 from CSII to MDI and one from MDI to 'injections TDS regime'. In one study site, four out of five patients who were randomised to MDI were changed to CSII and none from CSII to MDI, and, in another site, 9 out of 16 patients who were randomised to MDI were changed to CSII and 3 out of 14 changed from CSII to MDI. It is likely that there is a degree of bias towards CSII in these centres and this may account, in part, for the minor imbalance in movement between treatment arms. We also observed an imbalance in movement between treatment arms in the youngest age group, favouring a switch from MDI to CSII. This may also reflect a bias towards treatment with CSII in this age group, perhaps because of the difficulties of administering frequent injections in children in an age group who eat frequently and unpredictably throughout the day. The administration of very small insulin doses in the youngest children can also be difficult using MDI and this can be accommodated more easily using CSII.

When we examined the reasons for changing between treatment arms, we found that HbA_{1c} concentration was above the target range in 20 out of 22 patients (90.9%) at the time of changing from CSII to MDI and in 16 out of 30 patients (53%) at the time of changing from MDI to CSII. Severe or frequent hypoglycaemia was not reported as a reason for changing treatment arm. Our data suggest that, following randomisation, patient and parent preference was the strongest determinant of insulin delivery device.

Effectiveness of continuous subcutaneous insulin infusion and multiple daily injections therapy

Glycaemic control

We selected glycaemic control, measured as HbA_{1c} concentration 1 year after the diagnosis of T1D, as the primary outcome measure of treatment efficacy and the percentage of patients in whom HbA_{1c} concentrations were within the target range as a secondary outcome measure. Since the publication of the findings of the Diabetes Control Complications Trial Research Group,[3] HbA_{1c} concentration has been recognised as the most robust predictor of the risk of long-term T1D complications, and there is some evidence that this is particularly true during the first year after diagnosis.[7–9] Using this measurement of glycaemic control, we found no difference between treatment arms, at either 6 or 12 months following diagnosis. Previous RCTs comparing MDI and CSII have reported similar findings.[43,45,47,48] The significance of our results for the management of patients beyond 1 year is uncertain. However, there is good evidence that glycaemic control in the first year following diagnosis is a predictor of long-term glycaemic control and the risk of vascular complications in young adult life.[7–9]

A number of alternative outcome measures could have been used to compare the effectiveness of MDI and CSII, including glycaemic variability and preservation of pancreatic function. In vitro and animal studies have demonstrated that fluctuating glucose concentrations cause more cell damage and oxidative stress generation and induce monocyte–endothelial adhesion and atherogenesis to a greater degree than sustained hyperglycaemia.[137,138] It has also been reported that decreased, as well as increased, glycaemic variability may influence the expression of genes that protect cells from the toxic effects of hypoglycaemia, when compared with normal blood glucose profiles.[139]

Glycaemic variability has been seen to be lower in children treated with CSII than in those treated with MDI, despite there being no difference in HbA_{1c} concentrations.[32,140] In one cross-sectional cohort study, surrogate markers of oxidative stress and cyclo-oxygenase activity were also favourable and glycaemic control was superior in patients treated with CSII than in those treated with MDI. However, in studies in which treatment arms are not randomly assigned it may be difficult to determine whether the observed differences in glycaemic control and variability are a result of the mode of insulin delivery or patient characteristics that cluster with each treatment arm.

Although there is good evidence linking glycaemic variability and microvascular and macrovascular complications in type 2 diabetes, the evidence is less convincing for T1D.[141,142] This may be, in part, because the best measure of glycaemic variability (e.g. coefficient of variation of fasting plasma glucose, mean amplitude of glycaemic excursions, SD of blood glucose) has yet to be determined and because previous studies have used self-monitored blood glucose readings rather than continuous blood glucose monitoring. For now, it seems that HbA_{1c} concentrations remains the most appropriate primary outcome measure in studies of treatment effectiveness but measures of glycaemic variability should be considered as important secondary outcomes measures in future studies.

Partial remission and insulin dose

During the partial remission phase (PRP), there is some recovery of pancreatic islet cell function, insulin requirements fall and incidents of hypoglycaemia and hyperglycaemia occur less frequently and are less severe. Glycaemic control may be near perfect on minimal doses of insulin. In a study of over 3000 children with newly diagnosed T1D, approximately 70% experienced a PRP, which lasted 9 months (range 0–21 months). Younger age at diagnosis and female sex were associated with a lower prevalence of PRP.[143] Those who present with DKA or who have a lower pH or higher antibody titres at diagnosis are also less likely to experience PRP.

The longer-term implications of the PRP are unclear, although a recent study related PRP with the risk of microvascular complications; 7 years following diagnosis, young adults who did not experience a PRP were more likely to have one or more microvascular complication.[144]

A number of measures of beta cell function have been proposed for the definition of PRP, including measurements of basal and stimulated C-peptide.[145,146] However, these measurements require an early-morning attendance at hospital, which requires a delay in eating breakfast and the administration of the first morning dose of insulin. It may be especially difficult and inconvenient for patients treated with MDI to ensure an adequate 'washout' period following a dose of a long-acting insulin analogue for measurements of C-peptide to be meaningful.

In our original study protocol, we had not intended to undertake studies of residual pancreatic function. However, the publication of a new, validated method of assessing pancreatic reserve, based on insulin dose and HbA_{1c} concentration gave us the opportunity to explore this phenomenon in our population using data collected to inform other study outcomes.[147] This measure of residual pancreatic function was defined from a group of 275 patients aged < 16 years at diagnosis of T1D. Residual β-cell function was assessed by stimulated C-peptide measured 1, 6 and 12 months following diagnosis. To develop the definition, a multivariate analysis was performed, which demonstrated a negative correlation between stimulated C-peptide, HbA_{1c} concentration and insulin dose. From these observations, the authors developed a formula for $IDAA_{1c}$, in which a C-peptide response of > 300 pmol/l correlated well with $IDAA_{1c} \leq 9$ ($R^2 = 31\%$).

Using this method, $IDAA_{1c}$, we found no difference in the percentage of patients in PRP at either 6 or 12 months. When considering these data, it is important to note that the determination of $IDAA_{1c}$ relies on accurate recording of insulin doses.

For both treatment arms, insulin doses were downloaded from the F. Hoffman-La Roche AG Expert glucometer. For those randomised to CSII, insulin doses were also downloaded from insulin pumps and for those randomised to MDI data were obtained from patient-held records. The amount of insulin prescribed by the patients' family practitioners was also recorded. Data from these multiple sources showed that patients treated with MDI received significantly lower doses than those treated with CSII; this is in contrast to previous studies in which patients treated with MDI received higher doses of insulin.[35,46,82]

Patients randomised to the MDI arm of the study were advised that an insulin injection should be given every time ≥ 10 g of carbohydrates was consumed. It is likely that this will deter some patients from consuming carbohydrates between mealtimes. Patients randomised to the CSII arm of the study were given a lower threshold for the administration of an insulin bolus, 5 g of carbohydrate, in part because the administration of an insulin bolus is less intrusive than the administration of an injection. By giving this advice, we may have encouraged higher insulin usage in children treated with CSII.

Insulin usage differed between treatment arms only in patients aged ≥ 12 years, when those treated with CSII reported greater insulin use than those treated with MDI. This may reflect poorer reporting during adolescence and/or a reduction in the intensity of insulin injections as patients become increasingly independent.

Our data are subject to these methodological limitations, but, although recognising that these exist, we found no evidence that patients treated with CSII have lower insulin requirements than those treated with MDI or that the prevalence of the PRP was different between treatment arms at any time point.

Growth and weight gain

In common with previous studies, children recruited to the SCIPI study had a height SDS that was just above the mean (0.3, SD 1.0) of our reference population at diagnosis of T1D.[148] Growth during the first year of T1D was normal in both treatment arms and there was no difference in either baseline height SDS or change in height SDS between treatment arms.

Gain in weight has been reported to be greater in children treated with MDI than in those treated with CSII,[46] and this may be important, as obesity increases the risk of long-term macrovascular complications. In the SCIPI study protocol, baseline weight measurements were taken on the day that the randomised treatment was started, to allow time for adequate rehydration in children who were dehydrated at diagnosis. The baseline BMI SDS was normal and, similar to height SDS, it was just above the mean for the reference population (0.1, SD 1.3). In both treatment arms, BMI SDS increased: to 0.8 (SD 1.1) in the CSII arm and 0.7 (SD 1.0) in the MDI arm. This trend for weight gain may be of clinical concern if it continues in subsequent years.

Adverse events

The incidence of severe AEs was too low for us to draw any meaningful conclusions regarding the relative risk or benefits of either treatment. However, it is noteworthy that, of the 11 severe AEs that were reported (nine episodes of severe hypoglycaemia and two of DKA), nine occurred in patients treated with CSII. Previous RCTs have also reported a low prevalence of severe hypoglycaemia and DKA and concluded that there is no significant difference between treatment arms.[43–47]

It is possible that AEs were under-reported. This is unlikely for DKA but may be more likely for episodes of hypoglycaemia, which may be considered to be an inevitable part of T1D treatment. We recorded only severe hypoglycaemia, and frequent and less severe episodes of hypoglycaemia may also be debilitating.

A perceived advantage of CSII therapy is a reduction in the number of episodes of severe hypoglycaemia compared with treatment with MDI.[42,149] In 2010, *Health Technology Assessment* published a report that compared the clinical effectiveness and cost-effectiveness of CSII and MDI, which concluded that there were fewer problems with hypoglycaemic episodes in patients treated with CSII than those treated with MDI.[81] However, this systematic review included studies of MDI using Neutral Protamine Hagedorn insulin, which is associated with a higher incidence of hypoglycaemia than the insulin analogues used in modern MDI regimens.[71]

More than twice as many patients randomised to treatment with CSII as those randomised to treatment with MDI experienced AEs (28% vs. 10%, respectively), with the IDR being 24 for patients treated with CSII and 9 for patients treated with MDI.

A number of studies describing AEs during CSII therapy in childhood have been reported. In a large clinic population of 235 children, 45% of patients had experienced at least one insulin pump-related AE in the preceding 12 months, 8% required hospital treatment and 25% required a replacement insulin pump.[150] A very similar prevalence of CSII-related AEs (46% of treated patients) has been reported independently by another group,[151] and these data were supported further by a systematic review[152,153] of AEs in adult and childhood CSII therapy, which found that > 40% of patients per year had an insulin pump-related AE, with hyperglycaemia and DKA occurring most commonly. The risk of AEs is reported to be lower in those who have used CSII for longer, higher in children than in adults and unrelated to socioeconomic status or glycaemic control.[151]

We found no evidence of a reduced risk of severe hypoglycaemia, DKA or other AEs in patients treated with CSII.

Quality of life

It was our intention to minimise disruption to the routines of patients and the clinics in order to achieve a high level of recruitment and retention. For this reason, the number of additional tasks patients and parents were asked to perform was kept to a minimum. We decided to restrict assessments of QoL to a simple questionnaire-delivered tool, the diabetes module of the PedsQL instrument.[79] Patients who were aged ≥ 5 years completed questionnaires according to age (5–8, 9–12 and ≥ 13 years) and parents completed questionnaires for children aged 2–4, 5–8, 9–12 and ≥ 13 years.

We observed some discordance in the reports from parents and patients, as parents reported higher scores and, therefore, better QoL in those treated with CSII than in those treated with MDI but there was no difference in the scores reported by patients. The differences in parental scores were most notable in the youngest children, and particularly in the treatment domains for the youngest children.

Discordance in parental and patient reporting in measures of QoL is well recognised. In a large study[154] of 3402 children with T1D who were aged 5–18 years, which also used the PedsQL questionnaire, children reported a better QoL than that reported by their parent/proxy, except children aged 5–7 years in whom parent/proxy QoL reports were higher. The authors of this study concluded that both sources of reporting are valuable but that when discrepancies exist between patients and parent/proxy reports, preference should be given to the patient's report.[154]

Economic evaluation

The economic evaluation indicates that CSII does not represent a cost-effective option for the management of T1D in patients who were representative of the SCIPI study population. There was no evidence of a difference in QALY gain over the 12-month period of observation compared with MDI, and the cost differential was such that, even for willingness-to-pay values far in excess of the NICE £30,000 per QALY threshold for cost-effectiveness, CSII remained dominated by MDI.

The principal cost drivers, accounting for 91% of the difference between intervention groups, were the consumables and insulin pumps. These costs were not offset by any reduction in the prescribing of insulin or lower use of health-care services. In fact, patients who were randomised to CSII had more than twice as many A&E department visits and inpatient stays relating to the management of T1D as those in the MDI group. This may be attributable to the higher number of AEs associated with the use of CSII.

Sensitivity analyses confirmed the robustness of the results to different assumptions regarding the lifetime of the CSII insulin pump, the use of alternative methods for calculating utilities and of approaches to estimate the overall costs of insulin.

The analysis benefited from having complete cost data, achieved by obtaining resource use data from multiple sources, including routinely collected data and questionnaires. There were some missing responses to the HUI questionnaire, but different approaches of imputation and use of different tariff scores resulted in QALY estimates that were consistent with the base-case analysis. It should be acknowledged, however, that the trial was not powered to detect a statistically significant difference in QALYs between intervention groups.

The main limitation of the analysis concerns the short period of follow-up. The impacts of T1D and treatment modalities on QALYs are unlikely to be evident in the first year of treatment. Rather, QALY decrements are most likely to result from the long-term microvascular and macrovascular complications of T1D, and their associated impacts on health-related QoL and survival. In the absence of data from extended follow-up, the conventional approach of modelling life-long costs and consequences is usually taken. However, models that are not validated in paediatric populations, especially in the context of interventions that are not more clinically effective or likely to be cost-effective, would have limited credibility and offer little contribution to the understanding of longer-term economic outcomes.

Strengths and limitations

It is a major strength of the SCIPI study that a large and diverse population of patients has been recruited from a wide range of clinical settings across the UK, with near-complete retention at the conclusion of the study protocol. Our patient population is representative of the background population of patients diagnosed with T1D in study centres during the recruitment period of the study. We are confident that our data are generalisable to children treated for T1D in the NHS setting. Our recruitment strategy has also overcome the main sources of bias inherent in previous studies.

Using well-established and widely accepted measures of treatment effectiveness, we found no evidence that treatment of diabetes in the first year after diagnosis with CSII therapy is superior to treatment with MDI other than higher QoL on parent/proxy reporting.

We recruited patients at diagnosis of T1D to address important issues of bias inherent in some previous studies. However, our findings may not be applicable beyond the first year of diagnosis. The presence and duration of the PRP may mask subtle differences in therapeutic benefits and glycaemic control between treatment groups. Patient and parent education and knowledge may enable more sophisticated use of CSII over time and this may also confer an advantage compared with MDI in established patients, as suggested by some other studies.

We also recognise that the use of CSII at diagnosis of T1D was not routine practice at the time that the SCIPI study opened to recruitment, and outcomes may have improved over time as diabetes teams have gained experience in the use of this treatment modality. However, we also note that the primary outcome measurement was obtained 1 year after diagnosis, when all participants and professionals would have a minimum of 12 months' experience of both CSII and MDI, and was not a composite of measurements taken over the first year.

It is important to recognise that there is a strongly held view among health-care professionals, patients and families that CSII therapy is a valuable tool in the treatment of T1D, and is superior to treatment with MDI. It may be that we have not used the correct tools to identify the reasons for this or that the tools we have used are not sensitive enough to identify the benefits of treatment with CSII. This may be especially true for measures of QoL, and the absence of a measure of treatment satisfaction. Anecdotal reports from patients and parents often cite QoL as the main advantage of CSII therapy.

Qualitative work, examining the beliefs of physicians prescribing CSII, found there was acceptance that CSII therapy was not necessarily associated with superior glycaemic control compared with MDI.[155] This was attributed to the complexity of CSII therapy and the failure of patients and families to use it to its full potential, in part, owing to a lack of support in the community and at school. The same study found a strong attraction to CSII because of its status as a novel technology, as a necessary step towards more sophisticated and

successful therapies that should be embraced and encouraged. However, the authors also recognised that parents may feel pressurised to allow use of CSII in their children, given the strong advocacy for CSII therapy from support groups and some health-care providers. Perhaps most importantly, physicians reported social benefits of the use of CSII: allowing adolescent patients to become more independent and reducing parental stress around the unpredictable eating habits of young children and the need for frequent insulin injections. The physicians also felt that CSII therapy facilitated the physician–patient relationship. In order to fully understand the drivers behind the widespread adoption of CSII, tools will need to be developed that accurately harness this information.

Chapter 6 Conclusions

Implications for diabetes treatment strategies

The purpose of the SCIPI study was to generate objective data to inform national paediatric treatment strategies and individual patient care. We speculated that, in the absence of benefit of CSII therapy, resources may be better invested in services that are likely to benefit a wider range of patients.

In the NPDA of 2015/16,[1] 2800 children aged < 15 years were diagnosed with T1D. Given that 30% of patients are currently treated with CSII, our data suggest that the additional cost to the NHS of treating newly diagnosed patients with CSII in preference to MDI would reach approximately £1.5M per year, with no objective evidence of benefit, at least in the year following diagnosis.

The data from the SCIPI study should reassure families that there is no evidence that MDI therapy is inferior to CSII during the first year of T1D treatment. We have provided new evidence to clinicians that the driver for the adoption of CSII therapy at diagnosis of T1D should not be improved glycaemic control or AEs; indeed, we would encourage consideration of the increased prevalence of AEs in those treated with CSII.

The social benefits of CSII have not been quantified in this study, and perhaps the balance between cost and benefits in this domain is an issue for wider discussion between funders, health-care professionals, patients and families.

Future research

The findings of the SCIPI study may be applicable only during the first year following diagnosis of T1D. On completion of the study protocol, participants and their families were invited to consent for the collection of routine clinical data for a further 9 years. We therefore have the opportunity to learn more about the longer-term trajectories of this valuable and unique cohort of patients and whether or not outcomes diverge between treatment groups over time.

It is important to recognise that many patient advocacy groups and health-care professionals have a strong belief in the benefit of CSII. The measures of QoL used in the SCIPI study may not have been sensitive enough to detect the QoL benefits reported by the advocates of CSII, and we have not measured generic QoL or the impact of either treatment on social function across childhood and into adolescence. More detailed investigation in these domains may contribute to the critical analysis of the place of CSII in national diabetes strategies.

The need to examine how resources are distributed has become increasingly evident as relationships between socioeconomic status, CSII therapy and glycaemic control are reported. Observational cohort studies from across the world report superior glycaemic control and increased CSII use in children from more affluent families, and their parents have lower unemployment rates and higher educational levels than those children treated with MDI, whereas socioeconomic deprivation and ethnic minority status are associated with poor glycaemic control, independent of CSII use.[38,39,156,157] Unless efforts are made to correct this disparity, health-care resources will continue to be drawn away from the most vulnerable patients to support CSII therapy, with little evidence of benefit. We propose that research should now focus on interventions that may help to address the disparity in outcomes between the most affluent and disadvantaged children.

There is currently no validated, structured education programme for paediatric patients who are newly diagnosed with T1D, and previous studies of structured education have not demonstrated a beneficial effect on glycaemic control.[158] It may be that education to establish good management habits at the time of diagnosis will be more effective than in established patients, in whom poor management habits are likely to be entrained and instigating change may be difficult. The benefits of structured, validated education at diagnosis of T1D deserve further evaluation.

In this study, we did not record whether or not patients used CSII to its full potential. It is possible that enhanced CSII use would have resulted in improved glycaemic control and that this may be achievable through further education, training and support in the community. There may be a place for researching these elements of CSII use. However, such a package of care is likely to require increased investment, and this additional cost needs to be considered in the light of the health economic data reported in the SCIPI study. Very significant improvements in glycaemic control would be necessary for CSII to be seen as cost-effective. Should such a project be undertaken, it would be essential to also examine the effect of enhanced education and support in the community on glycaemic control in children treated with MDI.

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Contributions of authors

Joanne Blair (Chief Investigator and Consultant Paediatric Endocrinologist) developed the study protocol in collaboration with co-investigators. She oversaw the delivery of the study, prepared study update reports, oversaw clinical aspects of the statistical analysis plan and clinical interpretation of study data and led the preparation of the final report. She was Chairperson of the Trial Management Committee.

Carrol Gamble (Senior Statistician) contributed to the study design, protocol development, and data capture methods and led the CTU involvement including all monitoring activities, the development of the statistical analysis plan and the study statistical analyses. She contributed to the preparation of the final report (drafting, reviewing and editing).

Andrew McKay (Study Statistician) undertook the final statistical analyses under the supervision of Carrol Gamble, prepared data for reports throughout the study, prepared data tables and figures for the final report. He was a member of the Trial Management Committee.

Dyfrig Hughes (Lead Health Economist) contributed to protocol development, oversaw the health economic aspects of the study and the final analyses, contributed to the final report (drafting, reviewing and editing). He was a member of the Trial Management Committee.

Colin Ridyard (Health Economist) undertook health economics analysis, managed all aspects of health economics elements of the study, contributed to the final report (drafting, reviewing and editing). He was a member of Trial Management Committee.

Matthew Peak (Co-Investigator and Director of Research, Alder Hey Children's Hospital) contributed to protocol development, provided guidance on study delivery, supported interpretation of clinical data and contributed to the final report (drafting and reviewing). He was a member of the Trial Management Committee.

John W Gregory (Co-Investigator, Professor in Paediatric Endocrinology and Honorary Consultant) contributed to protocol development, provided guidance on study delivery, supported interpretation of clinical data and contributed to the final report (reviewing and editing). He was a member of the Trial Management Committee.

Mohammed Didi (Co-Investigator and Consultant Paediatric Endocrinologist) contributed to protocol development, provided guidance on study delivery, supported interpretation of clinical data and contributed to the final report (reviewer). He was a member of the Trial Management Committee.

Francesca Annan (Co-Investigator and Paediatric Diabetes Dietician) contributed to study design, prepared educational materials for study sites and contributed to the final report (reviewer).

Emma Bedson (Senior Trials Manager) gave guidance and support on all aspects of governance and study delivery and supported the preparation of progress reports. She contributed to the final report (reviewer) and was a member of the Trial Management Committee.

Keith Thornborough (RN and Paediatric Diabetes Nurse Specialist) recruited patients, provided guidance and expertise to RNs in study sites, led RN teleconferences and face-to-face meetings and supported interpretation of clinical study data. He contributed to the final report (reviewer) and was a member of the Trial Management Committee.

Publications

Blair JC, Peak M, Gregory JW. What is the best way to deliver subcutaneous insulin to infants, children, and young people with type 1 diabetes mellitus? *BMJ* 2011;**343**:d5221.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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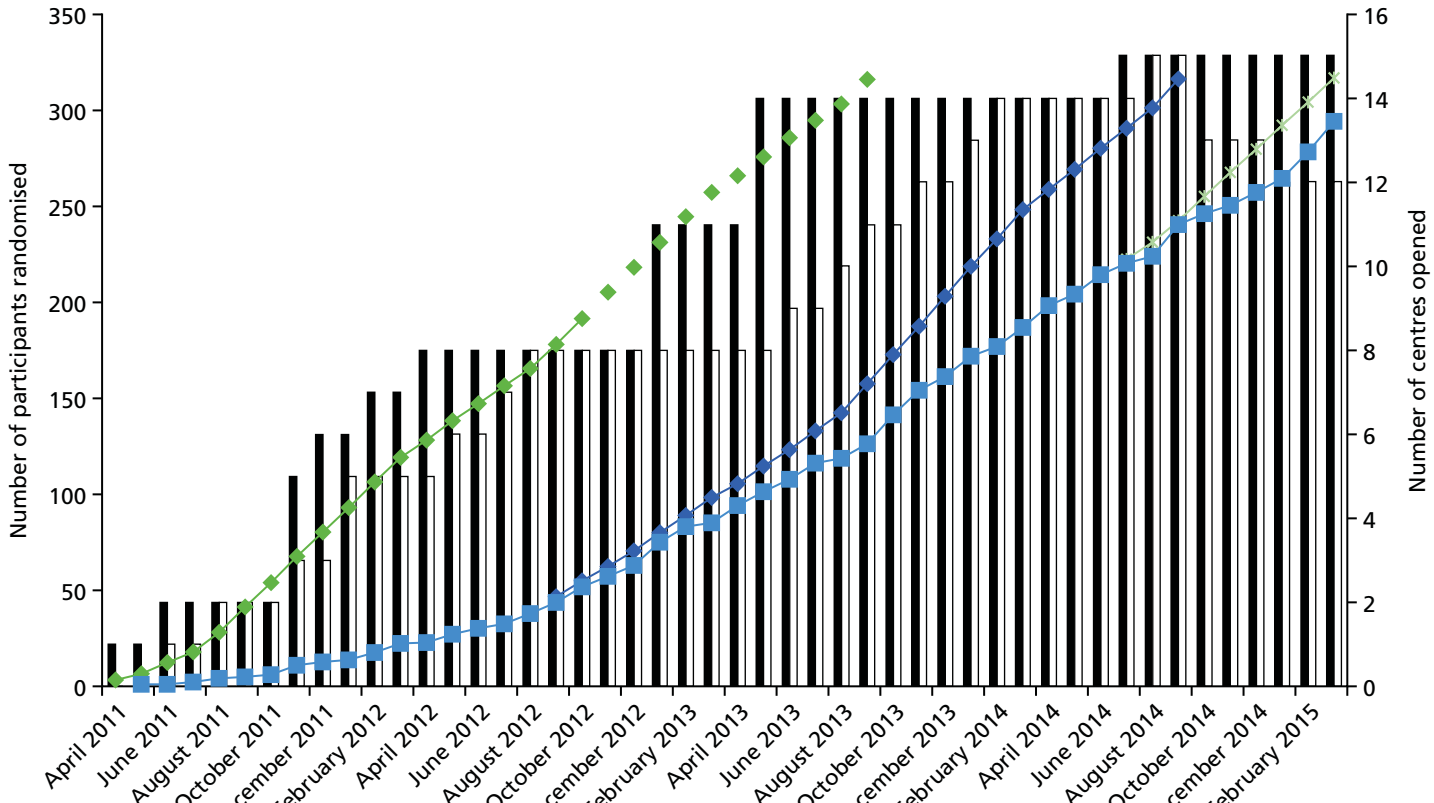
Appendix 1 Recruitment

Screening and consent by site with the affect of protocol amendments that were aimed to improve recruitment are provided in *Table 27*.



	April 2011	May 2011	June 2011	July 2011	August 2011	September 2011	October 2011	November 2011	December 2011	January 2012	February 2012	March 2012	April 2012	May 2012	June 2012	July 2012	August 2012	September 2012	October 2012	November 2012	December 2012	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015
Centres expected	1	1	2	2	2	2	2	5	6	6	7	7	8	8	8	8	8	8	8	8	8	11	11	11	11	14	14	14	14	14	14	14	14	14	14	14	14	14	14	15	15	15	15	15	15	15	15	15
Centres actual	0	0	1	1	2	2	2	3	3	5	5	5	5	6	6	7	8	8	8	8	8	8	8	8	8	8	9	9	10	11	11	12	12	13	14	14	14	14	14	14	15	15	13	13	13	12	12	12
Initial expected	3	6	12	18	28	41	54	67	80	93	106	119	128	138	147	156	165	178	191	205	218	231	244	257	266	275	285	294	303	316																			
Revised expected																		46	54	62	70	79	88	99	106	114	123	133	142	157	173	188	203	218	233	248	259	269	280	290	301	316							
Revised expected																																							223	231	243	255	267	280	292	304	316
Actual	1	1	1	2	4	5	6	11	13	14	18	22	23	27	30	32	38	44	52	57	63	75	83	85	94	101	108	116	119	126	141	154	161	172	177	187	198	204	214	220	224	240	246	250	257	264	278	294

FIGURE 11 Predicted and actual recruitment.

TABLE 27 Screening and consent by site (all protocol versions combined, but consent not sought broken down by protocol versions)

	[A]	[B]	[C]	[D]							[E]				[F]	
				Eligible but consent not sought							Eligible and consent sought but refused					
				Lack of trained staff (%) [dD]		Reason not recorded (%) [dD]		Consultant decision (%) [dD]								
Site (initiation date)	Total screens	Total not eligible (%) [dA]	Total eligible (%) [dA]	≤ version 3	≥ version 4	≤ version 3	≥ version 4	≤ version 3	≥ version 4	Total (%) [dC]	MDI preference (%) [dE]	CSII preference (%) [dE]	Other (%) [dE]	Total (%) [E]	Total consented (%) [dE + F]	Randomised
Total	976	98 (10)	878 (90)	18 (38.3)	34 (23.9)	0 (0)	22 (15.5)	29 (61.7)	86 (60.6)	189 (21.5)	259 (65.6)	36 (9.1)	100 (25.3)	395 (57.3)	294 (42.7)	294
Alder Hey (16 May 2011)	163	19 (11.7)	144 (88.3)	16 (94.1)	19 (55.9)	0 (0)	0 (0)	1 (5.9)	15 (44.1)	51 (35.4)	33 (80.5)	3 (7.3)	5 (12.2)	41 (44.1)	52 (55.9)	52
Newcastle (18 July 2011)	90	7 (7.8)	83 (92.2)	0 (0)	2 (18.2)	0 (0)	1 (9.1)	2 (100)	8 (72.7)	13 (15.7)	41 (69.5)	4 (6.8)	14 (23.7)	59 (84.3)	11 (15.7)	11
Birmingham (27 October 2011)	97	9 (9.3)	88 (90.7)	1 (5.9)	3 (15)	0 (0)	4 (20)	16 (94.1)	13 (65)	37 (42)	12 (40)	12 (40)	6 (20)	30 (58.8)	21 (41.2)	21
Cardiff (19 December 2011)	68	7 (10.3)	61 (89.7)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	2 (3.3)	34 (85)	1 (2.5)	5 (12.5)	40 (67.8)	19 (32.2)	19
Oxford (23 December 2011)	135	16 (11.9)	119 (88.1)	0 (0)	6 (40)	0 (0)	4 (26.7)	6 (100)	5 (33.3)	21 (17.6)	35 (56.5)	2 (3.2)	25 (40.3)	62 (63.3)	36 (36.7)	36
Doncaster (26 April 2012)	39	3 (7.7)	36 (92.3)	1 (50)	0 (0)	0 (0)	1 (33.3)	1 (50)	2 (66.7)	5 (13.9)	9 (75)	2 (16.7)	1 (8.3)	12 (38.7)	19 (61.3)	19
Southampton (12 June 2012)	77	11 (14.3)	66 (85.7)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)	12 (100)	15 (22.7)	14 (66.7)	0 (0)	7 (33.3)	21 (41.2)	30 (58.8)	30
Nottingham (20 July 2012)	86	7 (8.1)	79 (91.9)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	4 (80)	5 (6.3)	11 (84.6)	0 (0)	2 (15.4)	13 (17.6)	61 (82.4)	61
Blackburn (24 May 2013)	48	4 (8.3)	44 (91.7)	0 (0)	0 (0)	0 (0)	6 (60)	0 (0)	4 (40)	10 (22.7)	18 (78.3)	3 (13)	2 (8.7)	23 (67.6)	11 (32.4)	11
Mid Staffordshire (16 July 2013)	22	2 (9.1)	20 (90.9)	0 (0)	2 (33.3)	0 (0)	1 (16.7)	0 (0)	3 (50)	6 (30)	6 (50)	2 (16.7)	4 (33.3)	12 (85.7)	2 (14.3)	2
East Surrey (23 August 2013)	45	3 (6.7)	42 (93.3)	0 (0)	0 (0)	0 (0)	3 (50)	0 (0)	3 (50)	6 (14.3)	21 (75)	3 (10.7)	4 (14.3)	28 (77.8)	8 (22.2)	8
Ipswich (23 October 2013)	26	2 (7.7)	24 (92.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	6 (25)	6 (50)	1 (8.3)	5 (41.7)	12 (66.7)	6 (33.3)	6
Sheffield (4 December 2013)	32	5 (15.6)	27 (84.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (25)	2 (10)	13 (65)	20 (74.1)	7 (25.9)	7
Norfolk and Norwich (17 January 2014)	39	3 (7.7)	36 (92.3)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	7 (87.5)	8 (22.2)	11 (57.9)	1 (5.3)	7 (36.8)	19 (67.9)	9 (32.1)	9
Preston (10 July 2014)	9	0 (0)	9 (100)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	3 (75)	4 (44.4)	3 (100)	0 (0)	0 (0)	3 (60)	2 (40)	2

≤ version 3 refers to protocol versions 1–3 (covering recruitment period from 16 May 2011 to 16 August 2012) and ≥ version 4 refers to protocol versions 4–7 (covering recruitment period from 17 August 2012 to 31 March 2015). The columns [A]–[F] cells have been used for denominators in percentage calculations for other cells. [dx] denominator is [x]; [dx + y] denominator is [x] + [y].

TABLE 28 Demographic characteristics of screened patients

Demographic variable	Consent obtained	Patient declined		
		MDI preference	CSII preference	Other reason
Age (years)				
N	293	259	36	100
Mean	8.98	10	8.1	8.85
SD	4.13	3.76	4.27	4.09
Median	9.69	10.48	8.075	9.08
Minimum	0.7	0.41	1.28	0.98
Maximum	16	16	15.15	15.7
Missing (*n*)	1	0	0	0
Age, *n* (%)				
N	293	259	36	100
Birth to 6 months	0 (0)	1 (0.4)	0 (0)	0 (0)
7 months to 4 years	67 (22.9)	32 (12.4)	9 (25)	23 (23)
5–11 years	146 (49.8)	135 (52.1)	18 (50)	52 (52)
12–15 years	79 (27)	90 (34.7)	9 (25)	25 (25)
≥ 16 years	1 (0.3)	1 (0.4)	0 (0)	0 (0)
Missing	1	0	0	0
Sex, *n* (%)				
N	293	259	36	100
Female	140 (47.8)	121 (46.7)	17 (47.2)	46 (46)
Male	153 (52.2)	138 (53.3)	19 (52.8)	54 (54)
Missing	1	0	0	0
Ethnicity, *n* (%)				
N	292	259	36	100
Asian or Asian British	6 (2.1)	4 (1.5)	1 (2.8)	4 (4)
Black or British black	3 (1)	2 (0.8)	2 (5.6)	1 (1)
British white	242 (82.9)	228 (88)	25 (69.4)	81 (81)
Chinese	0 (0)	0 (0)	0 (0)	0 (0)
Indian	4 (1.4)	1 (0.4)	0 (0)	2 (2)
Mixed	10 (3.4)	6 (2.3)	2 (5.6)	1 (1)
Not stated	3 (1)	12 (4.6)	1 (2.8)	4 (4)
Other	5 (1.7)	1 (0.4)	0 (0)	1 (1)
Other white	14 (4.8)	3 (1.2)	1 (2.8)	5 (5)
Pakistani	5 (1.7)	2 (0.8)	4 (11.1)	1 (1)
Missing	2	0	0	0

TABLE 28 Demographic characteristics of screened patients (*continued*)

		Patient declined		
Demographic variable	Consent obtained	MDI preference	CSII preference	Other reason
Deprivation score[a]				
N	280	241	33	94
Mean	23.26	24.01	28.51	21.65
SD	18.53	18.19	16.57	16.17
Median	17.045	17.96	27.65	17.06
Minimum	1.62	1.18	3.9	2.95
Maximum	77.23	74.35	63.86	71.91
Missing (*n*)	14	18	3	6

a Deprivation score is measured from 0 to 100; 100 being worst possible deprivation.

Appendix 2 Supplementary results

Study or subgroup	CSII (switches to MDI) Events	Total	MDI (switches to CSII) Events	Total	Weight	Risk ratio M–H, fixed (95% CI)
00036 Norfolk and Norwich University Hospitals NHS	0	4	4	5	13.1%	0.13 (0.01 to 1.93)
00086 Doncaster Royal Infirmary	0	9	1	9	4.8%	0.33 (0.02 to 7.24)
00104 Stafford Hospital	0	0	0	2		Not estimable
00114 Southampton University Hospitals NHS Trust	3	14	9	16	26.8%	0.38 (0.13 to 1.14)
00133 Birmingham Children's Hospital	3	12	1	9	3.7%	2.25 (0.28 to 18.22)
00148 Ipswich Hospital	0	3	0	3		Not estimable
00160 Royal Preston Hospital	0	0	0	2		Not estimable
00213 Nottingham University Hospital NHS Trust	6	31	9	30	29.2%	0.65 (0.26 to 1.59)
00243 Alder Hey Children's NHS Foundation Trust	3	26	1	26	3.2%	3.00 (0.33 to 26.99)
00248 Sheffield Children's NHS Foundation Trust	1	4	0	3	1.8%	2.40 (0.13 to 44.41)
00326 East Surrey Hospital	0	3	2	5	6.4%	0.30 (0.02 to 4.74)
01527 Royal Blackburn Hospital	1	5	0	6	1.5%	3.50 (0.17 to 70.94)
04913 Cardiff and Vale University Local Health Board	0	9	0	10		Not estimable
05042 Oxford Radcliffe Hospitals NHS Trust	5	18	3	18	9.6%	1.67 (0.47 to 5.96)
12617 The Newcastle upon Tyne Hospitals NHS	0	6	0	5		Not estimable
Total (95% CI)		144		149	100.0%	0.78 (0.48 to 1.25)
Total events	22		30			

Heterogeneity: $\chi^2 = 9.58$, df = 9 ($p = 0.39$); $I^2 = 6\%$
Test for overall effect: $z = 1.05$ ($p = 0.30$)

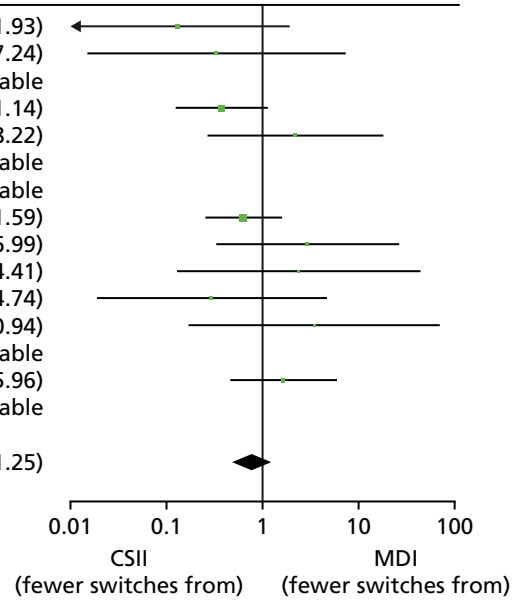


FIGURE 12 Permanent change to insulin delivery method split by site: forest plot (ITT). There were 53 permanent changes in total (22 were randomised to CSII and 31 were randomised to MDI). However, one permanent switch of insulin delivery method was from MDI to 'Injections TDS regime'. This has not been included in the meta-analysis as an event. M–H, Mantel–Haenszel.

TABLE 29 Permanent change to insulin delivery line listings[a]

Randomisation number	Timing of change (months)	Age at permanent change (years)	Last HbA_{1c} concentration measurement prior to switch (mmol/mol)	Person(s) who made decision	Reason(s)
Permanent change from CSII to MDI					
< 5 years					
00213102	0	1.84	110	Parent	Parent preference
5–11 years					
00243224	0–3	6.55	72	Patient	Participant preference
05042218	0–3	10.2	83	Patient	Participant preference
00213218	6–9	10.35	68	Clinician; parent; patient	Poor concordance with treatment
					Participant preference
					Parent preference
05042212	0–3	10.55	117	Parent; patient	Participant preference
					Parent preference
00114207	0–3	10.58	105	Parent; patient	Participant preference
					Parent preference
					Other: pain at cannula site
05042214	0	10.72	114	Clinician; parent	Poor glycaemic control – b. frequent hyperglycaemia
					Parent preference
00133207	6–9	10.8	N/A	Patient	Participant preference
00133209	9–12	11.24	58[b]	Patient	Participant preference
05042207	0	11.71	38	Parent; patient	Other: participant was not sure he wanted a pump to deliver insulin
00243219	0–3	11.95	98	Parent	Participant preference
≥ 12 years					
00133302	6–9	12.8	65	Parent; patient	Participant preference
					Parent preference
00114302	0–3	13.15	N/A	Parent; patient	Participant preference
					Parent preference
00213313	3	13.28	59	Clinician; parent; patient	Participant preference
					Parent preference
00213307	0–3	13.32	105	Parent; patient	Participant preference
					Parent preference
01527305	0–3	13.46	103	Parent; patient	Participant preference
05042301	0–3	14.05	129	Patient	Participant preference

continued

TABLE 29 Permanent change to insulin delivery line listings[a] (*continued*)

Randomisation number	Timing of change (months)	Age at permanent change (years)	Last HbA_{1c} concentration measurement prior to switch (mmol/mol)	Person(s) who made decision	Reason(s)
00213304	6–9	14.7	89	Clinician; patient	Poor concordance with treatment
00248302	0–3	14.95	126	Clinician; parent; patient	Participant preference
00213318	3	15.04	50	Patient	Participant preference
00114306	0–3	15.13	130	Clinician; parent; patient	Participant preference
00243313	9–12	15.38	63	Clinician; parent; patient	Poor glycaemic control – b. frequent hyperglycaemia Participant preference Parent preference
Permanent change from MDI to CSII					
< 5 years					
00213109	0–3	0.96	68	Clinician; parent	Other: age related
00036102	0–3	2.2	90	Parent	Parent preference
00243104	9–12	2.38	73	Clinician; parent	Poor glycaemic control – b. frequent hyperglycaemia Parent preference
00213101	3–6	2.66	66	Clinician; parent	Poor glycaemic control – a. debilitating hypoglycaemia Poor glycaemic control – b. frequent hyperglycaemia
00133104	9–12	3.42	72	Clinician	Poor glycaemic control – b. frequent hyperglycaemia
00213107	0–3	3.54	89	Clinician; parent	Poor glycaemic control – a. debilitating hypoglycaemia Parent preference
00213103	3–6	3.72	39	Clinician; parent	Other: young age needs smaller insulin quantities
00114105	9–12	3.98	79	Parent	Other: bruising from injections
00114101	3–6	4.15	51.9	Clinician; parent	Parent preference
05042104	6–9	4.47	60	Clinician; parent	Parent preference Other: frequent hypoglycaemia
00114103	6–9	4.78	78	Clinician; parent	Participant preference Parent preference
00036103	3–6	5.17	54	Clinician	Parent preference

TABLE 29 Permanent change to insulin delivery line listings[a] (*continued*)

Randomisation number	Timing of change (months)	Age at permanent change (years)	Last HbA_{1c} concentration measurement prior to switch (mmol/mol)	Person(s) who made decision	Reason(s)
5–11 years					
00114202	0–3	5.36	58.5	Clinician; parent; patient	Participant preference Parent preference
00086210	9–12	6.39	59	Clinician; parent; patient	Poor glycaemic control – b. frequent hyperglycaemia Participant preference Parent preference
00213229	6–9	7.64	51[b]	Clinician; parent	Poor concordance with treatment
00114206	3–6	7.67	46	Clinician; parent; patient	Participant preference Parent preference
00114213	6–9	8.01	53[b]	Parent; patient	Participant preference Parent preference
00326201	3–6	8.59	53	Patient	Participant preference
00114208	3–6	8.7	47	Clinician; parent; patient	Participant preference Parent preference
00213223	9–12	8.96	61	Clinician; parent; patient	Participant preference Parent preference
00326204	3–6	9.87	54[b]	Clinician; parent; patient	Participant preference
00213226	6–9	11.02	43[b]	Clinician; parent; patient	Poor concordance with treatment Participant preference Parent preference
05042217	9–12	11.42	58	Patient	Participant preference
00213211	3–6	12.02	43	Clinician; parent; patient	Participant preference Parent preference
00114209	6–9	12.31	64	Clinician; parent; patient	Participant preference Parent preference
05042216	9–12	12.42	44	Parent; patient	Participant preference Parent preference

continued

TABLE 29 Permanent change to insulin delivery line listings[a] (*continued*)

Randomisation number	Timing of change (months)	Age at permanent change (years)	Last HbA_{1c} concentration measurement prior to switch (mmol/mol)	Person(s) who made decision	Reason(s)
≥ 12 years					
00213306	3–6	12.61	38	Clinician; parent; patient	Participant preference Parent preference Other: fear of hypoglycaemia
00036303	0–3	12.69	133	Parent; patient	Participant preference Parent preference
00114301	3–6	14.44	38.8	Clinician; patient	Parent preference
00036301	6–9	15.69	32	Patient	Participant preference
Permanent change from MDI to injections TDS regime					
5–11 years					
12617501	9	10.06	66	Clinician; parent	Participant preference Parent preference

N/A, not applicable.
a Not prespecified analysis in the statistical analysis plan.
b NICE guidance changed in August 2015, lowering recommended HbA_{1c} concentrations from 58 mmol/mol to 48 mmol/mol. The date of permanent discontinuation was after the introduction of the lower threshold.

TABLE 30 Baseline characteristics for per-protocol analysis[a]

Baseline characteristic	Intervention arm		Total
	CSII	MDI	
Age at randomisation (years)			
n	87	66	153
Mean (SD)	8.6 (4.2)	9.7 (4.2)	9.1 (4.2)
Median (IQR)	9.1 (4.7–12.2)	10.1 (7.1–13.7)	9.3 (5.7–12.5)
Minimum, maximum	0.8, 16	0.9, 15.3	0.8, 16
Age (strata) category, *n* (%)			
n	87	66	153
7 months to < 5 years	23 (26.4)	11 (16.7)	34 (22.2)
5 years to < 12 years	41 (47.1)	32 (48.5)	73 (47.7)
12–15 years	23 (26.4)	23 (34.8)	46 (30.1)
Age category (EudraCT), *n* (%)			
n	87	66	153
Infants and toddlers	6 (6.9)	3 (4.5)	9 (5.9)
Children	58 (66.7)	40 (60.6)	98 (64.1)
Adolescents	23 (26.4)	23 (34.8)	46 (30.1)

TABLE 30 Baseline characteristics for per-protocol analysis[a] (*continued*)

Baseline characteristic	Intervention arm		Total
	CSII	MDI	
Sex, *n* (%)			
n	87	66	153
Female	44 (50.6)	29 (43.9)	73 (47.7)
Male	43 (49.4)	37 (56.1)	80 (52.3)
Ethnicity, *n* (%)			
n	86	65	151
Asian or Asian British	0 (0)	2 (3.1)	2 (1.3)
Black or British black	0 (0)	3 (4.6)	3 (2)
British white	78 (90.7)	51 (78.5)	129 (85.4)
Indian	2 (2.3)	1 (1.5)	3 (2)
Mixed	3 (3.5)	5 (7.7)	8 (5.3)
Not stated	0 (0)	0 (0)	1 (0.7)
Other	2 (2.3)	3 (4.6)	5 (3.3)
Pakistani	1 (1.2)	0 (0)	1 (0.7)
Deprivation score			
n	82	62	144
Mean (SD)	21.7 (18.9)	21 (16.8)	21.4 (18)
Median (IQR)	13.7 (8.4–31.8)	15.1 (8.4–30.9)	14.4 (8.4–31.4)
Minimum, maximum	2.1, 67.9	1.6, 73.9	1.6, 73.9

a Converse to prespecified analysis in the statistical analysis plan, which was to summarise baseline characteristics for those not included in the analysis.

TABLE 31 Child-reported QoL by domain[a]

Summary	Time point					
	6 months			12 months		
	CSII	MDI	Total	CSII	MDI	Total
Child (diabetes)						
Children 5–7 years old (6- and 12-month follow-up)						
n	12	22	34	14	19	33
Mean (SD)	56.8 (13.4)	61 (10.4)	59.5 (11.5)	66.7 (16.9)	59.6 (16)	62.6 (16.5)
Median (IQR)	54.5 (50–63.6)	59.1 (50–72.7)	56.8 (50–68.2)	68.2 (63.6–79.3)	63.6 (50–72.7)	63.6 (54.5–72.7)
Minimum, maximum	31.8, 81.8	40.9, 77.3	31.8, 81.8	27.3, 90.9	22.7, 77.3	22.7, 90.9

continued

TABLE 31 Child-reported QoL by domain[a] (*continued*)

Summary	Time point: 6 months CSII	6 months MDI	6 months Total	12 months CSII	12 months MDI	12 months Total
Children 8–12 years old (6- and 12-month follow-up)						
n	59	55	114	57	55	112
Mean (SD)	63 (16.9)	62.3 (15)	62.7 (15.9)	68.7 (15.8)	63.9 (16.1)	66.4 (16.1)
Median (IQR)	65.9 (49.6–77.3)	63.6 (50–74.4)	63.6 (50–75)	70.5 (54.5–79.5)	61.4 (50–77.3)	65.9 (52.3–79.5)
Minimum, maximum	25, 100	29.5, 100	25, 100	36.4, 100	37.2, 93.2	36.4, 100
Children 13–16 years old (6- and 12-month follow-up)						
n	29	31	60	37	33	70
Mean (SD)	68.2 (16.4)	64.3 (15.3)	66.2 (15.8)	62.9 (16.8)	61.6 (17.3)	62.3 (16.9)
Median (IQR)	65.9 (56.8–75)	61.4 (56.8–72.7)	63.6 (56.8–73.9)	61.4 (54.5–71.9)	59.1 (52.3–72.7)	61.1 (52.3–72.7)
Minimum, maximum	40.9, 100	40.9, 100	40.9, 100	27.3, 100	29.5, 90.9	27.3, 100
Child (treatment I)						
Children 5–7 years old (6- and 12-month follow-up)						
n	12	22	34	14	19	33
Mean (SD)	77.3 (18.3)	79.8 (16.1)	79 (16.7)	81.3 (16.8)	75.7 (22.2)	78 (20)
Median (IQR)	76.6 (62.5–93.8)	82.8 (75–87.5)	78.1 (75–87.5)	75 (75–100)	75 (62.5–87.5)	75 (62.5–100)
Minimum, maximum	50, 100	37.5, 100	37.5, 100	50, 100	12.5, 100	12.5, 100
Children 8–12 years old (6- and 12-month follow-up)						
n	59	54	113	57	55	112
Mean (SD)	79.3 (17.9)	74.7 (19.6)	77.1 (18.8)	83.7 (15.5)	77.2 (20.5)	80.5 (18.3)
Median (IQR)	87.5 (68.8–93.8)	75 (68.8–87.5)	81.3 (68.8–93.8)	87.5 (75–93.8)	81.3 (62.5–93.8)	81.3 (75–93.8)
Minimum, maximum	31.3, 100	12.5, 100	12.5, 100	25, 100	18.8, 100	18.8, 100
Children 13–16 years old (6- and 12-month follow-up)						
n	29	31	60	38	33	71
Mean (SD)	79.7 (21.2)	79.5 (14.2)	79.6 (17.8)	76.6 (21.2)	74.8 (15.3)	75.8 (18.6)
Median (IQR)	87.5 (75–93.8)	81.3 (75–87.5)	81.3 (75–93.8)	81.3 (68.8–93.8)	75 (62.5–87.5)	75 (68.8–87.5)
Minimum, maximum	6.3, 100	43.8, 100	6.3, 100	25, 100	31.3, 100	25, 100
Child (treatment II)						
Children 5–7 years old (6- and 12-month follow-up)						
n	12	22	34	13	19	32
Mean (SD)	80.1 (19.3)	83.2 (12.9)	82.1 (15.3)	82.3 (18.1)	79.9 (15.3)	80.9 (16.3)
Median (IQR)	85.7 (67.9–95.4)	83.7 (73.5–92.9)	85.7 (71.4–92.9)	85.7 (73.5–100)	78.6 (71.4–92.9)	80.1 (72.4–95.4)
Minimum, maximum	42.9, 100	57.1, 100	42.9, 100	35.7, 100	55.1, 100	35.7, 100

TABLE 31 Child-reported QoL by domain[a] (*continued*)

	Time point					
	6 months			12 months		
Summary	CSII	MDI	Total	CSII	MDI	Total
Children 8–12 years old (6- and 12-month follow-up)						
n	59	54	113	57	55	112
Mean (SD)	87.9 (11.9)	83.7 (14.5)	85.9 (13.3)	89.6 (11.6)	84.8 (17.6)	87.2 (15)
Median (IQR)	92.9 (82.1–96.4)	85.7 (77.6–96.4)	89.3 (78.6–96.4)	92.9 (82.1–100)	92.9 (75–100)	92.9 (82.1–100)
Minimum, maximum	45.9, 100	39.3, 100	39.3, 100	53.1, 100	16.3, 100	16.3, 100
Children 13–16 years old (6- and 12-month follow-up)						
n	29	31	60	38	33	71
Mean (SD)	90.1 (13.8)	87.2 (10.7)	88.6 (12.3)	84 (16.7)	85.3 (12.4)	84.6 (14.8)
Median (IQR)	96.4 (87.2–100)	85.7 (82.1–96.4)	92.9 (82.1–98)	91.3 (75–96.4)	85.7 (78.6–96.4)	89.3 (75–96.4)
Minimum, maximum	50, 100	60.7, 100	50, 100	42.9, 100	50, 100	42.9, 100
Child (worry)						
Children 5–7 years old (6- and 12-month follow-up)						
n	11	21	32	14	19	33
Mean (SD)	74.2 (26.2)	77.8 (24.9)	76.6 (25)	77.4 (31.1)	68.4 (28.8)	72.2 (29.7)
Median (IQR)	66.7 (66.7–100)	83.3 (66.7–100)	83.3 (66.7–100)	100 (50–100)	66.7 (50–100)	83.3 (50–100)
Minimum, maximum	16.7, 100	16.7, 100	16.7, 100	16.7, 100	0, 100	0, 100
Children 8–12 years old (6- and 12-month follow-up)						
n	59	54	113	57	53	110
Mean (SD)	81.2 (16.8)	75.8 (20.7)	78.6 (18.9)	82.5 (17.7)	78 (23.4)	80.3 (20.6)
Median (IQR)	83.3 (75–91.7)	79.2 (58.3–91.7)	83.3 (66.7–91.7)	83.3 (75–100)	83.3 (66.7–100)	83.3 (66.7–100)
Minimum, maximum	33.3, 100	25, 100	25, 100	16.7, 100	8.3, 100	8.3, 100
Children 13–16 years old (6- and 12-month follow-up)						
n	29	31	60	38	33	71
Mean (SD)	80.5 (22.1)	77.2 (17.9)	78.8 (19.9)	73 (23.2)	74.5 (23.3)	73.7 (23.1)
Median (IQR)	83.3 (66.7–100)	83.3 (66.7–91.7)	83.3 (66.7–91.7)	75 (50–100)	75 (58.3–100)	75 (50–100)
Minimum, maximum	25, 100	33.3, 100	25, 100	33.3, 100	25, 100	25, 100
Child (communication)						
Children 5–7 years old (6- and 12-month follow-up)						
n	11	22	33	14	18	32
Mean (SD)	56.1 (38.2)	77.3 (23.9)	70.2 (30.5)	57.1 (33.1)	80.6 (25.7)	70.3 (31)
Median (IQR)	50 (16.7–100)	83.3 (66.7–100)	66.7 (50–100)	58.3 (33.3–83.3)	83.3 (66.7–100)	75 (50–100)
Minimum, maximum	0, 100	33.3, 100	0, 100	0, 100	0, 100	0, 100

continued

TABLE 31 Child-reported QoL by domain[a] (*continued*)

Summary	Time point					
	6 months			12 months		
	CSII	MDI	Total	CSII	MDI	Total
Children 8–12 years old (6- and 12-month follow-up)						
n	58	55	113	54	54	108
Mean (SD)	82.2 (18.3)	72 (25.3)	77.2 (22.5)	79.7 (23.7)	75.6 (26.6)	77.6 (25.2)
Median (IQR)	83.3 (75–100)	75 (58.3–91.7)	83.3 (66.7–100)	91.7 (66.7–100)	83.3 (58.3–100)	83.3 (58.3–100)
Minimum, maximum	16.7, 100	0, 100	0, 100	8.3, 100	0, 100	0, 100
Children 13–16 years old (6- and 12-month follow-up)						
n	29	29	58	38	33	71
Mean (SD)	86.2 (15.5)	81.6 (19.7)	83.9 (17.7)	81.6 (18.1)	76.8 (26.4)	79.3 (22.3)
Median (IQR)	91.7 (75–100)	83.3 (75–100)	87.5 (75–100)	83.3 (66.7–100)	83.3 (66.7–100)	83.3 (66.7–100)
Minimum, maximum	50, 100	16.7, 100	16.7, 100	33.3, 100	0, 100	0, 100

a Not prespecified in the statistical analysis plan to present data at 6 months.

TABLE 32 Parent-reported QoL by domain[a]

Questionnaire age group	Time point					
	6 months			12 months		
	CSII	MDI	Total	CSII	MDI	Total
Parent (diabetes)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	25	18	43	22	18	40
Mean (SD)	62 (16)	58.1 (11.1)	60.4 (14.1)	62.7 (17.1)	56.2 (16.2)	59.8 (16.8)
Median (IQR)	62 (54.5–65.9)	58.1 (47.7–65.9)	61.4 (47.7–65.9)	59.1 (47.7–75)	56.8 (43.2–68.2)	56.8 (46.6–72.7)
Minimum, maximum	27.3, 97.7	38.6, 75	27.3, 97.7	33.1, 97.7	27.3, 81.8	27.3, 97.7
Parents/carers: children aged 5–7 years old (6- and 12-month follow-up)						
n	14	23	37	17	18	35
Mean (SD)	66.2 (12)	61.4 (13.9)	63.2 (13.2)	68.3 (15.4)	60.8 (15.7)	64.5 (15.8)
Median (IQR)	65.9 (59.1–77.3)	59.1 (50–72.7)	61.4 (54.5–72.7)	65.9 (56.8–77.3)	61.4 (53.7–72.7)	65.9 (53.7–75)
Minimum, maximum	43.2, 84.1	38.6, 90.9	38.6, 90.9	45.5, 95.5	13.6, 81.8	13.6, 95.5

TABLE 32 Parent-reported QoL by domain[a] (*continued*)

	Time point					
	6 months			12 months		
Questionnaire age group	CSII	MDI	Total	CSII	MDI	Total
Parents/carers: children aged 8–12 years old (6- and 12-month follow-up)						
n	58	58	116	55	55	110
Mean (SD)	62.9 (14.9)	62.7 (15.3)	62.8 (15)	66.2 (14.6)	60.8 (16.2)	63.5 (15.6)
Median (IQR)	63.6 (52.3–75)	61.4 (52.3–72.7)	61.4 (52.3–72.7)	65.9 (52.3–75.2)	61.4 (47.7–74.4)	63.6 (52.3–75)
Minimum, maximum	25, 93.2	36.4, 95.5	25, 95.5	43.2, 100	29.5, 97.7	29.5, 100
Parents/carers: children aged 13–16 years old (6- and 12-month follow-up)						
n	30	29	59	38	34	72
Mean (SD)	63.9 (17.4)	60.3 (18.1)	62.1 (17.7)	60.3 (17.7)	61.5 (14)	60.9 (15.9)
Median (IQR)	58 (52.3–81.8)	61.4 (50–72.7)	59.1 (52.1–75)	59.1 (47.7–68.2)	61.4 (54.5–70.5)	61.4 (50–70.5)
Minimum, maximum	36.4, 97.7	24.8, 100	24.8, 100	27.3, 100	22.7, 90.9	22.7, 100
Parent (treatment I)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	25	18	43	21	18	39
Mean (SD)	79.8 (20.5)	69.8 (20.7)	75.6 (20.9)	80.7 (18.9)	73.6 (20.8)	77.4 (19.9)
Median (IQR)	87.5 (62.5–100)	68.8 (56.3–93.8)	75 (56.3–100)	87.5 (68.8–93.8)	81.3 (68.8–87.5)	81.3 (68.8–87.5)
Minimum, maximum	37.5, 100	31.3, 100	31.3, 100	31.3, 100	18.8, 100	18.8, 100
Parents/carers: children aged 5–7 years old (6- and 12-month follow-up)						
n	14	23	37	17	18	35
Mean (SD)	63.8 (28.4)	69.3 (19.2)	67.2 (22.9)	72.8 (21.5)	69.8 (21.1)	71.3 (21.1)
Median (IQR)	62.5 (50–87.5)	68.8 (56.3–81.3)	68.8 (56.3–81.3)	81.3 (56.3–87.5)	71.9 (56.3–87.5)	75 (56.3–87.5)
Minimum, maximum	0, 100	31.3, 100	0, 100	37.5, 100	25, 100	25, 100
Parents/carers: children aged 8–12 years old (6- and 12-month follow-up)						
n	58	57	115	55	55	110
Mean (SD)	71.3 (20.3)	67.9 (20.8)	69.6 (20.5)	69.1 (18.7)	66.9 (19.6)	68 (19.1)
Median (IQR)	75 (56.3–87.5)	68.8 (56.3–87.5)	68.8 (56.3–87.5)	68.8 (56.3–81.3)	62.5 (56.3–81.3)	68.8 (56.3–81.3)
Minimum, maximum	25, 100	12.5, 100	12.5, 100	25, 100	25, 100	25, 100
Parents/carers: children aged 13–16 years old (6- and 12-month follow-up)						
n	30	29	59	38	34	72
Mean (SD)	65.2 (22.3)	61.3 (18.1)	63.3 (20.3)	67.3 (22.1)	62.3 (21.9)	64.9 (22)
Median (IQR)	68.8 (43.8–81.3)	62.5 (50–75)	62.5 (50–81.3)	68.8 (50–81.3)	62.5 (43.8–81.3)	68.8 (50–81.3)
Minimum, maximum	25, 100	31.3, 100	25, 100	25, 100	12.5, 100	12.5, 100

continued

TABLE 32 Parent-reported QoL by domain[a] (*continued*)

Questionnaire age group	Time point: 6 months CSII	6 months MDI	6 months Total	12 months CSII	12 months MDI	12 months Total
Parent (treatment II)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	25	18	43	22	18	40
Mean (SD)	85.4 (13.6)	74.2 (16.6)	80.8 (15.7)	88.6 (10.9)	82.7 (14.8)	85.9 (13)
Median (IQR)	91.8 (82.1–96.4)	73.2 (61.2–85.7)	82.1 (69.4–96.4)	92.3 (85.7–92.9)	87.8 (75–93.9)	90.8 (80.4–93.4)
Minimum, maximum	49, 100	40.8, 100	40.8, 100	59.7, 100	45.9, 100	45.9, 100
Parents/carers: children aged 5–7 years old (6- and 12-month follow-up)						
n	14	23	37	16	18	34
Mean (SD)	84.2 (14.4)	82.8 (9.8)	83.3 (11.6)	84.8 (14.3)	77.6 (15.3)	81 (15.1)
Median (IQR)	91.3 (75–96.4)	82.1 (75–92.9)	85.7 (75–93.9)	85.7 (70.2–100)	76.8 (64.3–92.9)	82.1 (65.3–96.4)
Minimum, maximum	57.1, 98	64.3, 100	57.1, 100	64.3, 100	50, 98	50, 100
Parents/carers: children aged 8–12 years old (6- and 12-month follow-up)						
n	58	58	116	55	55	110
Mean (SD)	86.4 (12.7)	80.9 (15.3)	83.7 (14.3)	86.8 (13.5)	81.1 (16.6)	83.9 (15.3)
Median (IQR)	87.2 (77.6–98)	82.1 (71.4–92.9)	85.7 (73.5–96.4)	89.3 (81.6–100)	85.7 (67.9–92.9)	89.3 (75–96.4)
Minimum, maximum	50, 100	39.3, 100	39.3, 100	44.9, 100	16.3, 100	16.3, 100
Parents/carers: children aged 13–16 years old (6- and 12-month follow-up)						
n	29	29	58	38	34	72
Mean (SD)	84.6 (15.1)	79.4 (15)	82 (15.1)	80.7 (16.4)	77.7 (19.6)	79.3 (17.9)
Median (IQR)	85.7 (77.6–98)	82.1 (64.3–92.9)	85.7 (73.5–93.9)	81.9 (64.3–96.4)	78.6 (67.9–92.9)	81.6 (67.9–96.4)
Minimum, maximum	42.9, 100	55.1, 100	42.9, 100	39.3, 100	32.1, 100	32.1, 100
Parent (worry)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	25	18	43	21	18	39
Mean (SD)	63 (29.5)	45.4 (28.6)	55.6 (30.1)	47.9 (28.1)	48.6 (31.9)	48.2 (29.5)
Median (IQR)	58.3 (33.3–91.7)	41.7 (25–58.3)	50 (33.3–83.3)	41.7 (33.3–75)	54.2 (25–66.7)	50 (25–75)
Minimum, maximum	8.3, 100	0, 100	0, 100	0, 100	0, 100	0, 100
Parents/carers: children aged 5–7 years old (6- and 12-month follow-up)						
n	14	23	37	17	18	35
Mean (SD)	61.3 (26.7)	75.4 (22)	70 (24.5)	61.3 (29.3)	67.1 (25.2)	64.3 (27)
Median (IQR)	58.3 (33.3–83.3)	83.3 (58.3–91.7)	75 (50–91.7)	66.7 (33.3–83.3)	75 (50–83.3)	75 (41.7–83.3)
Minimum, maximum	25, 100	25, 100	25, 100	16.7, 100	0, 100	0, 100

TABLE 32 Parent-reported QoL by domain[a] (*continued*)

	Time point					
	6 months			12 months		
Questionnaire age group	CSII	MDI	Total	CSII	MDI	Total
Parents/carers: children aged 8–12 years old (6- and 12-month follow-up)						
n	58	58	116	55	55	110
Mean (SD)	72.1 (20.1)	64.4 (21.3)	68.2 (21)	68.2 (24.3)	67.7 (25.3)	68 (24.7)
Median (IQR)	75 (58.3–83.3)	66.7 (50–83.3)	66.7 (50–83.3)	75 (50–91.7)	66.7 (50–91.7)	70.8 (50–91.7)
Minimum, maximum	25, 100	25, 100	25, 100	8.3, 100	0, 100	0, 100
Parents/carers: children aged 13–16 years old (6- and 12-month follow-up)						
n	30	29	59	38	34	72
Mean (SD)	69.2 (24.4)	65.2 (23.5)	67.2 (23.8)	71.9 (21)	66.9 (23.6)	69.6 (22.3)
Median (IQR)	75 (50–91.7)	66.7 (50–83.3)	66.7 (50–83.3)	75 (50–83.3)	75 (50–83.3)	75 (50–83.3)
Minimum, maximum	8.3, 100	16.7, 100	8.3, 100	33.3, 100	8.3, 100	8.3, 100
Parent (communication)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	24	19	43	21	17	38
Mean (SD)	83.7 (25.2)	74.1 (28.7)	79.5 (26.9)	81.3 (25.7)	70.6 (34)	76.5 (29.8)
Median (IQR)	100 (75–100)	75 (58.3–100)	91.7 (66.7–100)	91.7 (75–100)	83.3 (50–100)	91.7 (50–100)
Minimum, maximum	0, 100	0, 100	0, 100	25, 100	0, 100	0, 100
Parents/carers: children aged 5–7 years old (6- and 12-month follow-up)						
n	13	23	36	17	17	34
Mean (SD)	82.7 (22.4)	84.1 (22.5)	83.6 (22.1)	72.5 (32.1)	80.9 (18.8)	76.7 (26.3)
Median (IQR)	100 (66.7–100)	91.7 (75–100)	95.8 (75–100)	83.3 (50–100)	83.3 (66.7–100)	83.3 (66.7–100)
Minimum, maximum	41.7, 100	16.7, 100	16.7, 100	0, 100	41.7, 100	0, 100
Parents/carers: children aged 8–12 years old (6- and 12-month follow-up)						
n	58	57	115	54	55	109
Mean (SD)	78.7 (22.4)	75.7 (26.2)	77.2 (24.3)	80.1 (22.8)	67.2 (26.3)	73.6 (25.4)
Median (IQR)	83.3 (66.7–100)	83.3 (58.3–100)	83.3 (58.3–100)	87.5 (75–100)	75 (50–91.7)	75 (58.3–100)
Minimum, maximum	16.7, 100	0, 100	0, 100	0, 100	0, 100	0, 100
Parents/carers: children aged 13–16 years old (6- and 12-month follow-up)						
n	29	28	57	38	34	72
Mean (SD)	77 (28.9)	67.3 (24.1)	72.2 (26.9)	73.2 (26.1)	72.8 (30.7)	73 (28.2)
Median (IQR)	83.3 (75–100)	66.7 (50–91.7)	83.3 (50–100)	75 (50–100)	79.2 (58.3–100)	75 (58.3–100)
Minimum, maximum	0, 100	25, 100	0, 100	0, 100	0, 100	0, 100

continued

TABLE 32 Parent-reported QoL by domain[a] (*continued*)

	Time point					
	6 months			12 months		
Questionnaire age group	CSII	MDI	Total	CSII	MDI	Total
Parent (overall)						
Parents/carers: children aged 2–4 years old (6- and 12-month follow-up)						
n	24	18	42	20	17	37
Mean (SD)	72.5 (13)	64 (11.5)	68.9 (12.9)	73 (12.7)	67 (15.7)	70.2 (14.3)
Median (IQR)	72.8 (62.9–77.2)	61.8 (55.5–74.1)	68.8 (57–76.8)	75 (62.1–82.1)	70.5 (54.7–79.5)	73.2 (60.7–80.4)
Minimum, maximum	54.5, 98.6	46.7, 81.6	46.7, 98.6	52.4, 99.1	40.2, 90.2	40.2, 99.1

a Not prespecified in the statistical analysis plan to present data at 6 months.

Appendix 3 Health economics analysis plan

This health economic analysis plan provides a detailed and comprehensive description of the pre-planned economic analyses for the SCIPI study. The planned economic analysis described within this document is compliant with those specified in brief within the SCIPI study protocol version 6.0 (16 February 2016). This health economic analysis plan comprehensively describes the planned final analysis.

These planned analyses will be performed by health economists at the Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK.

All analyses will be performed using Stata version 13 and reported according to CHEERS.

Overview

Within the SCIPI study, the cost-effectiveness of CSII compared with insulin administered subcutaneously by MDI will be assessed from a UK NHS perspective. The cost-effectiveness will be based on the incremental cost per QALY gained. The economic analysis will have two parts: (1) a trial-based evaluation of the first 12 months from diagnosis and, if one intervention is clinically superior, (2) a lifetime extrapolation of costs and outcomes, based on an economic model of diabetes.

Data sources

Resource use

Data on health-care resource use are based on:

- PLICS data and/or PAS data of participating hospitals.
- The trial CRFs, which will record health-care resource items (outpatient visits, primary care and hospital stays) for the 3 months prior to randomisation at baseline and then at 3, 6, 9 and 12 months following randomisation. All hospital stays will be measured irrespective of whether or not they are related to diabetes.
- Prescription records, patient diaries and electronic downloads from pumps, to estimate the number of units of insulin used by patients.

Unit costs

All resource use will be valued in monetary terms using UK unit costs current at the time of analysis. HRGs will be used as the main currency of the economic analysis for inpatient stays with cost codes allocated based on the latest available national tariff. Obsolete national tariff and schedule codes will be uplifted using the hospital price index according to the current version of the compendium of *Unit Costs of Health and Social Care*.[123] This resource will also be the source of unit costs that will be applied to primary health-care and outpatient contacts.

Bundled national tariff costs will be based on the hospital spell and incorporated excess ward days, market forces factor and whether the case was elective or emergency. Tariff codes will be obtained primarily from PLICS and PAS data but if unavailable they will be assigned by reference to CRFs and an appropriate HRG code will be assigned based on condition and comorbidities. Similarly, appropriate HRGs will be applied to unassignable national tariff HRG codes appearing in the PLICS and PAS data.

Unbundled costs such as intensive care unit stays are not expected to be common; however, if they do arise they will be identified from reference to (1) lists of AEs, (2) CRF code 4 critical care, (3) PLICS data or

(4) PAS data. Appropriate HRG codes for unbundled costs will be assigned from the National Schedule of reference costs.[122]

Insulin and concomitant medication costs will be based on those detailed in the *British National Formulary*.[124]

Utilities

Within-trial health utilities will be estimated from patients' (aged ≥ 12 years) and their parents' or guardians' responses to the HUI questionnaire and the application of UK tariff scores.

Data analysis

Costs

Within-trial total costs for each patient will be calculated from the sum of ward, outpatient, A&E, primary care, disposable devices, insulin and concomitant medication usage. An annualised cost will be assigned for the insulin pump and accoutrements.

Costs at baseline, relating to the 3 months preceding randomisation, will be calculated from CRF data with reference to PAS and PLICS data when available. This will relate to all primary and secondary care activity.

If a hospitalisation is observed for the period subsequent to randomisation, an adjustment may be necessary to apportion costs, given that ward costs relate to episodes of care that could start prior to randomisation. Patients admitted to hospital n days before randomisation and spending N days in hospital after randomisation will have their total costs calculated as:

$$\text{Total cost} = (N/n + N) \times (\text{ward cost derived from HRG}). \quad (6)$$

Patients' use of health-care resources and total costs will be calculated for the ITT population, with summary statistics generated by intervention group. Differences between intervention groups in mean lengths of stay and costs will be compared with reference to bias-corrected and accelerated bootstrapped 95% CIs, based on 10,000 replicates.

Imbalances in baseline covariates, should any be present in spite of randomisation, may result in biased estimates of cost-effectiveness. If there are imbalances in important clinical or demographic variables, we will implement suitable regression techniques.

Outcomes

A QALY profile over the 12-month trial period will be estimated from HUI2/HUI3 derived utilities based on the area under the curve, assuming the trapezoidal rule.

Incremental analysis

The trial-based cost-effectiveness analysis of CSII will be evaluated by its ICER, which will be calculated according to:

$$\text{ICER} = \Delta\text{Costs}/\Delta\text{QALY}. \quad (7)$$

where ΔCosts is the difference in total costs between interventions (cost CSII – cost MDI), and ΔQALY is the difference in utility between interventions (QALY CSII – QALY MDI).

Uncertainty analysis

The joint uncertainty in costs and outcomes at 12 months will be considered by non-parametric bootstrapping resampling (10,000) of patient costs and QALYs. Uncertainty will be represented using a cost-effectiveness acceptability curve to present the probability of CSII being cost-effective for given ceiling thresholds for costs

per QALY gained. Estimates of ICERs will be compared with the £20,000–30,000-per-QALY threshold of cost-effectiveness set by NICE.

Sensitivity analyses

A range of sensitivity analyses will be considered, including different calculations for estimating the costs of pumps, use of alternative (Canadian) tariff scores for the HUI3 algorithm and application of MICE for imputing missing cost and utility data, when necessary.

Exploratory analyses

The contribution of baseline variables to total costs and QALYs will be examined using regression models. Given the expected skewed nature of outcomes, we will specify generalised linear models using (1) total cost per patient and (2) total QALYs per patient, as the dependent variable, and explanatory variables for accounting for baseline cost, baseline HbA_{1c} concentration, age, centre and other covariates, as specified in the statistical analysis plan, as well as the intervention group. The Modified Park test will be used to identify the preferred distributional family based on the lowest chi-squared test value. For each prediction model, the link function will be identified using the Pearson correlation test, the Pregibon link test and the modified Hosmer–Lemeshow test. When all three tests yield non-significant *p*-values, the link function is said to fit well.

If there are significant differences in HbA_{1c} concentrations between intervention groups at 12 months, we will conduct an exploratory analysis in which trial results will be extrapolated to estimate lifetime costs and benefits and to capture long-term microvascular and macrovascular complications, using the CDM. We acknowledge that the CDM has not been validated for populations comparable with those in the SCIPI study; however, this exploratory analysis will aim to assess potential lifetime benefits and incremental cost per QALY of tighter glycaemic control in early diagnosed paediatric patients with T1D.

The CDM will be initialised with a cohort profile consistent with each intervention group of the SCIPI study, in terms of demographic and clinical characteristics. A conservative estimate of treatment effect having been reached at 12 months from randomisation will be assumed to calculate the risk factor trajectories over time for blood pressure, lipids and HbA_{1c} concentration using the default setting of the UK Prospective Diabetes Study (UKPDS) panel equations. Costs inbuilt to the CDM will be used to estimate lifetime total cost per patient. Costs and QALYs in the extrapolated phase will be discounted at 3.5% per annum.

Appendix 4 Patient and public involvement

We have aimed to describe patient and public involvement throughout this report. A summary is provided below.

We have worked with young people and parent contributors from study design to delivery.

The MCRN group of children and young people, 'Stand Up, Speak UP!', advised us on the contents and presentation of patient information leaflets and consent forms.

Three parent contributors were recruited to the TMG, which met by teleconference every month, and one parent contributor joined the TSC. Our parent contributors were particularly valuable during the recruitment period of the study. They advised us of the impact of the diagnosis of T1D and how and when to approach patients and their families in a sensitive manner, and helped us to anticipate barriers to recruitment.

When it became evident that recruitment rates were significantly influenced by patient preference for MDI, we approached completed participants from both arms of the study to participate in the study video. Participants and their parents shared their experiences of the diagnosis of T1D and of living with their randomised treatment and their reasons for participating in clinical research. This video was very well received by health-care professionals, families and patients.

Once recruitment rates had been optimised, we entered a phase of the study in which the TMG discussions focused on issues relating to governance and internal study management. During this period, it was more difficult to engage our parent contributors and to ensure that the discussions were relevant and interesting to them.

As results became available, we invited our parent contributors to help us to interpret them and set them in the context of living with childhood T1D. These discussions have been very helpful and have motivated us to learn more about our study cohort, in particular how the experiences of those treated with MDI and CSII may have differed in ways that were not identified through the study questionnaires. The importance of extending the observation period was also discussed. We will apply for further funding to undertake this research in the near future, and we hope to continue to work with our parent contributors to develop and deliver new study protocols.

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